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MINIREVIEW

Regulation of metabolism in *Caenorhabditis elegans* longevity

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Abstract

The nematode *Caenorhabditis elegans* is a favorite model for the study of aging. A wealth of genetic and genomic studies show that metabolic regulation is a hallmark of life-span modulation. A recent study in *BMC Biology* identifying metabolic signatures for longevity suggests that amino-acid pools may be important in longevity.

Aging in *Caenorhabditis elegans* seems to be intimately tied to the modulation of metabolism. The first genes identified for their ability to affect life span were *age-1*, which encodes a phosphatidylinositol kinase [1], and *daf-2* (constitutive dauer formation), which encodes a receptor tyrosine kinase similar to the mammalian insulin and insulin-like growth factor 1 (IGF1) receptors [2]. Although complete loss of *daf-2* function is lethal [3], partial loss of function extends adult life by two- to threefold. *daf-2* and *age-1* specify steps in the insulin/insulin-like signaling (IIS) pathway, thereby influencing metabolism. IIS signaling inactivates the FOXO (forkhead box O) transcription factor DAF-16, which controls genes that mediate a wide variety of functions, including metabolism, innate immunity, stress response, and translation (reviewed in [4]). The modulation of life span by the IIS pathway seems to result from an intricate network of physiological changes primarily mediated by unregulated DAF-16 activity, including major shifts in both energy and fat metabolism.

In addition to the IIS pathway, two other main groups of genes have profound effects on life span and are linked to metabolic control: genes involved in dietary restriction and mitochondrial function. Dietary restriction has been associated with increased life span in a wide variety of species (including mammals) and appears to be universally associated with longevity (reviewed in [5]). Increased longevity resulting from mutations in genes that regulate mitochondrial function is more problematic, although, at least superficially, it is related to metabolic slow-down. Work in nematodes and other invertebrates seems to support the notion that reducing the rate of oxidative phosphorylation (OXPHOS) leads to increased life span in two major ways: by decreasing the metabolic rate, and by reducing the level of reactive oxygen species, which are an obligate byproduct of OXPHOS. However, mutations that reduce mitochondrial function are beneficial for *C. elegans* longevity, but have deleterious and often lethal effects in mammals [6]. The reason for this discrepancy is not understood.

Given the large number of genes that have been shown to regulate life span through different pathways, it is reasonable to ask whether there are any physiological changes conducive to longevity that are common in all long-lived mutants. A recent metabolomic study on five different long-lived mutants published in *BMC Biology* by Fuchs *et al.* [7] suggests that the answer to this question may be yes. Fuchs *et al.* report that mutants carrying three different alleles of *daf-2*, one allele of the insulin-like gene *daf-28* or one allele of *ife-2* (translational initiation factor 4E) have similar metabolic signatures, which cluster away from those of wild-type worms. These metabolic signatures are consistent with previous findings that assessed gene expression in *daf-2* mutants [8]. In particular, they showed that long-lived *daf-2* worms upregulate the glyoxylate cycle, gluconeogenesis and starch metabolism.

Fuchs *et al.* [7] detected a common metabolic signature for IIS mutants and *ief-2*. All five of the long-lived mutants had increased pools of amino acids, especially of the branched-chain amino acids isoleucine, leucine and valine, together with phenylalanine and tyrosine. A similar increase in branched-chain amino acids has been found in animals carrying mutations in components of

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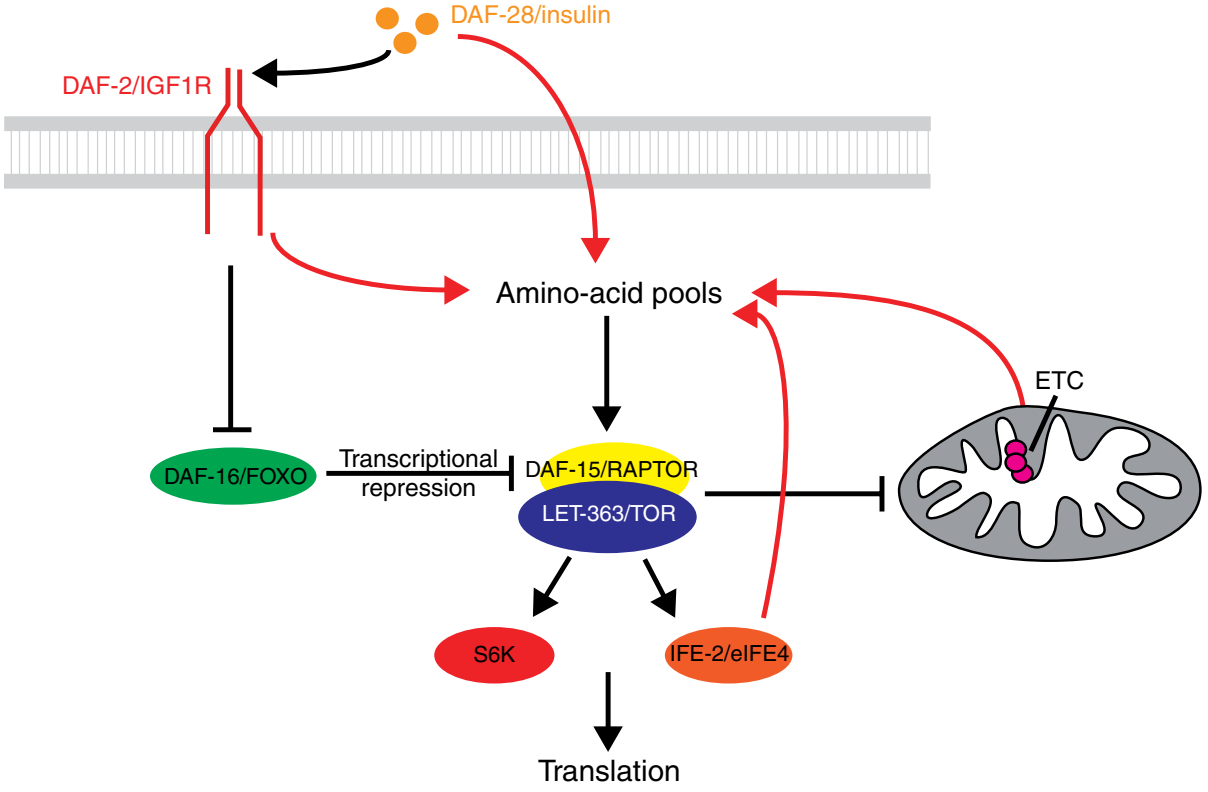

Figure 1. Possible link between accumulation of amino-acid pools, mitochondrial function, and the insulin and TOR pathways in *C. elegans* longevity. Black lines indicate the activating or repressive function of members of different signal transduction pathways. Amino-acid pools and other nutrients activate TOR signaling, which then results in increased translation following activation of the protein kinase S6K and the translation initiation factor eIFE4 and inhibition of mitochondrial biogenesis. However, mutations in DAF-2/IGF1R result in the activation of DAF-16, which represses *daf-15* transcription to reduce TOR signaling. Red arrows indicate the effects of mutations on cellular amino-acid pools. Specifically, Fuchs *et al*. [7] show that mutations in *daf-2/IGF1R*, *daf-28/insulin* and *ife-2/eIFE4* cause an increase in amino acid levels, especially branched-chain amino acids. Falk *et al*. [9] showed that mutations affecting complexes I, II and III of the electron transport chain (ETC), including some that increase life span, also result in accumulation of branched-chain amino acids. Mutations that confer longevity through different pathways share the metabolic signature of increased branched-chain amino-acid pools.

the mitochondrial electron transport chain (ETC) complexes I, II and III [9]. At least some of these ETC mutants are long-lived. The increase in branched-chain amino acids in long-lived worms is intriguing for two reasons. First, it opens the possibility that protein metabolism plays an important role in life-span determination. Second, branched-chain amino acids are known to stimulate protein synthesis and inhibit protein degradation in higher eukaryotes [10], a phenomenon mediated by the TOR (target of rapamycin) pathway.

Dietary restriction and metabolism

Although it might seem reasonable to assume that dietary restriction exerts its life-prolonging effects by reducing metabolic function, recent reports argue to the contrary (reviewed in [11]). Worms on a dietary restriction regimen induced genetically (by *eat* mutations), or by dilution of nutrients, or by exposure to axenic medium (medium that supports growth without bacteria), actually had increased metabolic rates, as measured by oxygen consumption and heat production. The mechanism by which dietary restriction regulates life span in worms is therefore not clear. While it seems to act by regulating the insulin pathway in *Drosophila* and rats, the IIS pathway is not responsible for dietary-restriction-induced longevity in *C. elegans*.

The most likely pathway exploited by dietary restriction in *C. elegans* is the TOR pathway. The physiological role of TOR kinase is to sense nutrient levels - such as cellular amino-acid pools - and to regulate transcription and protein biogenesis and degradation accordingly. TOR exists in two highly conserved protein complexes: TORC1, which regulates cell growth, protein synthesis and autophagy; and TORC2, which regulates cytoskeletal reorganization [12]. Both complexes regulate the metabolic state of *C. elegans*. TOR activates the ribosomal p70 S6 kinase (S6K) and the translation initiation factor eIF4E. The latter is encoded by *ife-2* in *C. elegans*, and a

mutant in this gene was studied in the metabolomic analysis performed by Fuchs *et al.* [7]. It was previously observed that knockdown of *TOR*/*let-363* pathway in *C. elegans* results in an almost twofold increase in life span [13]. Although not mentioned by Fuchs *et al.* [7], their metabolic profiles fit very well with a model whereby TOR modulates life span via *ife-2*: downregulation of TOR increases longevity; *ife-2* is an effector of the TOR pathway and animals carrying a mutation in this gene also live longer; and *ife-2* mutants accumulate pools of amino acids that are known to induce protein biogenesis and inhibit protein degradation. These data naturally lead to the speculation that the longevity of IIS mutants is at least partially derived from downregulation of TOR.

Mutation of DAF-15/RAPTOR, an activator of TOR, results in increased *C. elegans* life span [13]. Interestingly, *daf-15* is directly regulated by DAF-16, the ultimate effector of the IIS pathway. It was therefore proposed that mutations reducing IIS signaling (such as *daf-2* mutations) activate DAF-16, which then represses *daf-15* to decrease the function of TOR and enhance longevity (Figure 1). The increased amino-acid pools found by Fuchs *et al.* [7] in the IIS mutants *daf-2* and *daf-28* could be explained by the consequent downregulation of TOR, which in turn would result in decreased translation and consequent accumulation of amino-acid pools. Mutations in *ife-2* would also result in increased amino-acid pools.

Branched-chain amino acids and longevity

Fuchs *et al.* [7] may, in fact, hold a clue to one of the mysteries of the aging field: why do translation-defective mutants live longer? If translation mutants such as *ife-2* accumulate amino acids, they would mimic the conditions arising in mitochondrial ETC mutants and IIS pathway mutants. TOR pathway mutants would be predicted to have very similar metabolic profiles to ETC, *daf*-2 or *ife-2* mutants. Analyzing the metabolomes of TOR mutants and translation-defective mutants could therefore shed some light on this problem.

In conclusion, the belief that decreased metabolism leads to longevity is, so far, a generalization that extends beyond the current evidence. We know that genes involved in metabolic control, such as *daf-2*, regulate life span, but we do not know if overall metabolism is downregulated in these mutants [11]. For instance, *daf-2* mutants exhibit decreased carbohydrate metabolism, but gene-expression data suggest that lipid utilization pathways are actually upregulated in these mutants [8].

Life-span-prolonging effects of downregulating protein synthesis might be specific to *C. elegans* and other invertebrates. The soma of the adult nematode is post-mitotic, and metabolic control might have different effects in *C. elegans* (where adult cell and tissue replacement does not occur) from those in higher eukaryotes, where compromised cells can be eliminated by apoptosis and replaced. *C. elegans* cells might have a higher tolerance for cellular insults and decreased metabolism. It is conceivable that translation of new proteins and other cell-maintenance processes may be more important to *C. elegans* than to higher organisms, as *C. elegans* somatic cells cannot be replaced.

Although the role of metabolism in aging is not straightforward, the metabolomics of longevity mutants may provide some answers. It is interesting to notice that several classes of long-lived mutants - mitochondrial ETC mutants, IIS mutants, and translation mutants - all have increased levels of branched-chain amino acids [7,9]. Metabolomic profiles of TOR pathway mutants, dietary restriction mutants and other translation mutants could reveal an under-appreciated function of amino-acid metabolism in longevity.

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