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.
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/RAF, 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 postmitotic, 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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