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The Energy Maintenance Theory of Aging: maintaining energy metabolism to allow longevity

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Abstract

Fused, elongated mitochondria are more efficient in generating ATP than fragmented mitochondria. In diverse *C. elegans* longevity pathways, increased levels of fused mitochondria are associated with lifespan extension. Blocking mitochondrial fusion in these animals abolishes their extended longevity. The long-lived *C. elegans vhl-1* mutant is an exception that does not have increased fused mitochondria, and is not dependent on fusion for longevity. Loss of mammalian VHL upregulates alternate energy generating pathways. This suggests that mitochondrial fusion facilitates longevity in *C. elegans* by increasing energy metabolism. In diverse animals, ATP levels broadly decrease with age. Substantial evidence supports the theory that increasing or maintaining energy metabolism promotes the survival of older animals. Increased ATP levels in older animals allow energy-intensive repair and homeostatic mechanisms such as proteostasis that act to prevent cellular aging. These observations support the emerging paradigm that maintaining energy metabolism promotes the survival of older animals.

Keywords

lifespan; energy metabolism; *C. elegans*; mitochondria; mitochondrial fusion

1. Introduction

Since its initiation as a model organism over 50 years ago, *Caenorhabditis elegans* has proven to be an important model for biological research owing to its small size, simplicity, and outstanding genetic tools. *C. elegans* has been an ideal system to study lifespan due to their short lifespan of two to three weeks. Many genome-wide screens have been conducted in *C. elegans* to identify genes and pathways that extend lifespan.^[1–4] Many of the *C. elegans* lifespan extension pathways are conserved in yeast, flies, mice, and humans.^[1, 5, 6] The first major lifespan extension mutants identified in *C. elegans* were for the insulin signaling pathway, and these mutants live over twice as long as wild-type animals.^[7] Subsequently, insulin signaling has been shown to broadly affect lifespan in other animals.^[6]

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Apart from insulin signaling, multiple other pathways have been identified that regulate lifespan, some of which molecularly overlap with insulin signaling, while others induce longevity through distinct mechanisms.^[8] Here we will focus on recent work that suggests an underlying mechanism that allows the survival of older animals in response to these diverse pathways. We will discuss evidence supporting a model that the diverse longevity pathways incorporate mechanisms (such as altering mitochondrial morphology) to maintain ATP levels and energy homeostasis in order to allow the survival of older animals. Broader evidence suggests that the requirement to maintain energy metabolism to allow longevity extends to other animals.

2. Mitochondria are important determinants of aging

Much like the endosymbiotic origin of mitochondria that is shared by all eukaryotes, it has been suggested that a decline in mitochondrial function with aging is also a shared eukaryotic trait.^[9] Mitochondria have been recognized to be a central player in aging for over five decades, and are considered to be the organelle that is most affected by aging.^[10] Many aspects of mitochondria change as mammals age, including respiration rate, enzyme levels, overall mitochondrial mass, and morphology.^[9, 11, 12] As an example, 95% of mitochondria in the muscle tissue of a healthy 90-year-old man were found to be damaged, compared to no detectable damage in the muscle tissue of a 5-year-old child.^[13] Impairment of mitophagy, the pathway to eliminate mitochondria, also occurs with age; and this can contribute to the accumulation of damaged mitochondria with mitochondrial DNA (mtDNA) mutations.^[14] Consistently, increased mitophagy is protective for mitochondrial health, and is associated with decreased cellular aging in mice and humans and increased lifespan in *C. elegans* and *Drosophila*.^[14, 15]

A recent study has shown that mitochondria in senescent cells contribute significantly to the aging phenotypes associated with senescence.^[16] mtDNA mutations increase in humans as they age, and are correlated with aging and cellular aging phenotypes.^[17] Maternally-inherited mtDNA mutations have been linked to age-related diseases and shortened lifespan.^[18–20] Mice that were engineered to have a proofreading-deficient mtDNA polymerase, and hence accumulate mtDNA mutations at a much higher rate, have accelerated aging.^[21]

Large-scale RNAi screens in *C. elegans* revealed that the largest class of genes regulating lifespan are those encoding mitochondrial proteins,^[2, 3, 22] with the largest proportion of these affecting the electron transport chain (ETC).^[2, 23] Inactivation of ETC genes can shorten or extend lifespan. Intriguingly, ETC mutants with extended lifespans exhibit increased levels of mitochondrial fusion.^[3] Mitochondria are dynamic organelles that can fuse with each other or fragment through processes termed fusion and fission, respectively. Mitochondrial dynamics are required for proper mitochondrial function.^[24] As *C. elegans* adults age, their mitochondria become increasingly fragmented.^[25, 26]

3. Increased levels of elongated mitochondria are broadly associated with longevity in *C. elegans*

The largest extension of lifespan in *C. elegans* from a single genetic modification comes from inactivating the insulin signaling pathway.^[7, 27] Lifespan extension through this pathway requires the FoxO transcription factor DAF-16, which regulates the expression of genes required for longevity. We discovered a molecular pathway by which DAF-16 regulates mitochondrial fusion. In this pathway, DAF-16 represses the expression of two mitochondrial m-AAA proteases that negatively regulate the levels of the mitochondrial fusion protein EAT-3/OPA1.^[28] Inactivation of insulin signaling leads to the activation of DAF-16, and the resulting repression of the m-AAA proteases causes an increase in the levels of EAT-3/OPA1 and mitochondrial fusion. Long-lived insulin-signaling mutants have increased levels of elongated (fused) mitochondria as a result of activating this pathway. Surprisingly, blocking mitochondrial fusion (by RNAi of the inner mitochondrial membrane fusion protein EAT-3/OPA1) in insulin receptor mutants eliminated the lifespan extension, resulting in a lifespan similar to that of wild type. Inactivating the inner mitochondrial fusion protein in a wild-type background had no discernable effect on lifespan. This suggests that increased mitochondrial fusion is required for the considerable lifespan extension of insulin-pathway mutants.

C. elegans lifespan can be extended by altering multiple cellular pathways. Strikingly, nine of ten different pathways that extend lifespan showed increased mitochondrial fusion.^[28] Similar observations of increased mitochondrial fusion were observed by other research groups for five of these longevity pathways: ETC dysfunction; mitochondrial unfolded protein response (UPRmt); activation on AMP-activated protein kinase (AMPK); caloric restriction; and inhibition of insulin signaling.^[3, 26, 29, 30, 31] Significantly, the extended lifespans for the nine pathways are dependent on increased mitochondrial fusion. Blocking mitochondrial fusion through inactivation of the inner mitochondrial fusion protein EAT-3 made their lifespans similar to that of wild type.^[28] Notably, increasing fusion by itself does not significantly extend lifespan.^[26, 29] Thus, increased mitochondrial fusion appears to be required to maintain the survival of older animals whose lifespan is extended in response to other cellular pathways.

Interestingly, increasing mitochondrial fusion in budding yeast extends both replicative and chronological lifespan.^[32] Further, inhibiting mitochondrial fusion in budding yeast shortens lifespan.^[33] Thus, the promotion of longevity by increased mitochondrial fusion extends to other eukaryotes beyond *C. elegans*.

4. Is increased mitochondrial fusion a proxy for increased energy metabolism in extending longevity?

Our results demonstrated a requirement for increased mitochondrial fusion in the survival of older *C. elegans*. It is likely that the modification of one or more mitochondrial functions is responsible for the lifespan extension, rather than fusion itself. In that situation, it should be possible to decouple the requirement for fused mitochondria from lifespan extension. One

potential illustration of this is that a different genetic combination to block insulin signaling and mitochondrial fusion, i.e., a mutation of the outer fusion protein FZO-1/Mfn with RNAi of the insulin receptor/*daf-2*, did not reduce the extended lifespan associated with insulin receptor RNAi.^[29] In contrast, RNAi of the inner fusion protein significantly reduced the lifespan of an insulin receptor mutant.^[28] It is possible that the different methods of altering mitochondrial morphology (i.e., inactivating inner vs. outer fusion proteins) in combination with partial or complete insulin pathway inactivation differentially affects mitochondrial function(s). Clearly, further research is required to provide insights into how these manipulations affect cristae structure and mitochondrial activities in order to distinguish the relevant functional effects that contribute to aging. Nevertheless, these results suggest that the survival of older animals is not always linked to mitochondrial fusion, but may instead be linked to an attribute that is generally associated with elongated mitochondria.

A mutant that was an exception to the rule provides a clue that the key aspect of elongated mitochondria in allowing longevity is increased energy generation. Of the 10 lifespan extension pathways that we analyzed, only one did not exhibit increased levels of elongated mitochondria: *vhl-1* mutants. Unlike the other longevity pathways, blocking mitochondrial fusion in *vhl-1* mutants did not shorten their extended lifespan.^[28] VHL-1 is the *C. elegans* ortholog of the mammalian von Hippel Lindau tumor suppressor (VHL).^[34] VHL is a substrate receptor for cullin-RING ubiquitin ligase 2 (CRL2) complexes. The CRL2^{VHL} ubiquitin ligase targets the degradation of the hypoxia-inducible factor 1 α transcription factor (HIF1A/HIF-1 α) under normal oxygen conditions. When HIF1A is not degraded during hypoxia, it induces the expression of genes that allow cells to survive the reduced-oxygen conditions.^[35]

Why would the *vhl-1* mutant be less reliant on mitochondrial fusion than other longevity mutants? And does this exception give us any clues about how increased mitochondrial fusion allows the survival of older animals in the other longevity pathways? Elongated mitochondria are generally more efficient in generating ATP than fragmented mitochondria.^[36] A striking connection between VHL and energy metabolism comes from work with human tissue culture cells. A genome-wide CRISPR knockout screen was carried out for mutations that allow tissue culture cell survival after blocking mitochondrial ETC activity.^[37] The top gene knockout that allowed cells to survive the loss of mitochondrial ATP production was the *VHL* gene. This inherently makes sense, as loss of VHL activates HIF1A to allow cells to survive under hypoxic conditions in which there is a greatly reduced level of oxygen, which is required for mitochondrial respiration. This pathway appears to be conserved in *C. elegans*. The activation of HIF-1 is required for the lifespan extension of *vhl-1* mutants.^[34] And inactivation of *C. elegans* VHL-1 leads to the activation of HIF-1, which induces the expression of genes that promote glycolysis, similar to what is observed in mammals.^[35, 38] ATP levels in *C. elegans vhl-1* mutants have not yet been reported, but the upregulation of glycolytic enzymes in *vhl-1* mutants is likely to promote energy generation independently of mitochondria, as occurs in mammalian cells.^[37, 39]

These results lead to the hypothesis that mitochondrial fusion promotes *C. elegans* longevity by increasing ATP levels via increased mitochondrial respiratory efficiency. Strikingly, the very long-lived insulin-pathway mutants have ATP levels that are over two-fold higher than

in wild-type animals.^[28, 40] Other long-lived mutants with elongated mitochondria also have increased ATP levels.^[28] In support of the position that ATP levels are more important than the type of mitochondrial morphology in determining lifespan, it was shown in *Drosophila* adults that mitochondrial fission (rather than fusion) is associated with increased lifespan, and this was correlated with an increase in oxidative phosphorylation.^[41] Additionally, inhibiting both fusion and fission (so that the mitochondria maintain their normal morphology) increases lifespan in *C. elegans*, and also is associated with increased oxidative phosphorylation.^[29] These studies further the correlation between ATP generation and longevity, and also illustrate that elongated mitochondria are not the only morphology type associated with increased energy metabolism.

One potential argument against this hypothesis is the question of how mutations in ETC complex components can extend lifespan in *C. elegans* – because ETC mutations would be expected to have reduced mitochondrial ATP production. However, the lifespan extension that is associated with mutating ETC components is actually an indirect mechanism that involves the UPR^{mt}. Mutating ETC complex genes induces the UPR^{mt}, which contributes to their extended lifespans.^[42] An initial clue that the lifespan extension is indirect came from the observation that activating the UPR^{mt} only extends lifespan if the activation occurs during the larval developmental stages, while lifespan is not extended if UPR^{mt} activation occurs solely in adults.^[22] It was subsequently found that during larval stages, UPR^{mt} in neurons triggers a systemic response that induces changes in chromatin in other tissues, and the altered transcriptional changes mediate lifespan extension.^[43] Therefore, the UPR^{mt} lifespan extension is not directly associated with the ETC dysfunction (but instead arises from secondary transcriptional changes). These transcriptional changes may increase energy metabolism, as several ETC mutants exhibit ATP levels that are the same as wild type or increased.^[44]

While ETC mutants invoke extended longevity through a mechanism that involves transcriptional changes, it is unclear why ETC mutants require increased mitochondrial fusion for longevity.^[28] Increased mitochondrial fusion may be contributing to other aspects of longevity that do not involve ATP production. However, it is also possible that even when there is a loss-of-function for an ETC component, elongated mitochondria can improve the generation of ATP through cellular respiration. In this regard, it has been shown that increased mitochondrial fusion allows continued, stable ATP production in animals with RNAi inactivation of ETC complex IV components.^[45]

5. Evidence that maintaining ATP levels and energy metabolism supports longevity

As adult *C. elegans* age, ATP levels decrease steadily and dramatically, with the ATP levels in very old adults only ~20% of the level in young adults.^[46] Most longevity studies with *C. elegans* do not analyze ATP. However, those studies that have analyzed ATP levels have shown that increased ATP levels in adults accompanies the lifespan extension in a variety of genetic backgrounds and experimental treatments (Table 1).

Reductions in energy metabolism are broadly associated with aging in many animals.^[47] ATP levels in human calf muscles decrease at approximately 8% per decade.^[12] Similarly, ATP levels decrease with age in cardiac muscles in humans, mice, and rats;^[48] and in mice retina and brain.^[49] ATP levels in *Drosophila* also decrease with age, with older animals having approximately 50% lower ATP levels than younger animals.^[50]

Separating mice into quartiles based on metabolic intensity showed that the quartile with the highest metabolism lived 36% longer than the animals in the lowest quartile.^[51] This indicates that in mice, greater energy metabolism is associated with longer lifespan. Experimentally increasing ATP levels in *Drosophila*, by exposure to near-infrared light that activates cytochrome c oxidase, leads to a modest increase in lifespan.^[52]

A cohort of studies demonstrates the beneficial effects of exercise, which is associated with an increase in ATP metabolism. Currently, among the best intervention to slow down age-related decline in muscle function is physical exercise.^[53] Accumulating evidence from epidemiological studies and randomized clinical trials suggests that regular physical activity and endurance exercises reduce occurrences of age-related pathologies, including sarcopenia, type 2 diabetes, decline in cardiovascular and cognitive functions, telomere length, stem cell exhaustion, and senescence.^[12, 53, 54] Female rats that undergo voluntary exercise live longer despite an increase in food intake.^[55] In *C. elegans*, exercise extends lifespan, and this is associated with mitochondrial fusion.^[28, 56] Aerobic exercise has been shown to enhance muscle mtDNA abundance in both human and mouse, and increase ATP levels.^[12, 57]

In mammals, increases in mtDNA mutations accelerate aging.^[13] Because many mtDNA genes are required directly or indirectly for oxidative phosphorylation, increases in mtDNA mutations negatively impact ATP production.^[19] Human diseases associated with maternally-inherited mitochondrial mutations have accelerated aging and shortened lifespan.^[18] Over 250 of such ‘pathogenic’ mtDNA mutations have been identified, and these have invariably been found to be associated with decreased ATP levels.^[58] A recent study has shown that inducing mitophagic clearance of mitochondria in human cells can reverse the aging phenotypes of cellular senescence. Surprisingly, these cells, despite having fewer mitochondria, had higher ATP levels due to the upregulation of glycolytic enzymes.^[16] This work therefore decouples the need for mitochondria from the potentially beneficial effects of increased ATP levels. Treatments of cells with acetyl-L-carnitine or ubiquinone alleviate aging-related phenotypes; and while these treatments affect multiple aspects of mitochondria, they also increase ATP production.^[11]

Notably, diseases that induce symptoms of accelerated aging are also associated with lower ATP levels. Fibroblasts from patients with Progeria show a 50% reduction in ATP levels compared to healthy individuals.^[59] A mouse model of Werner syndrome (known as adult Progeria) exhibits 40% lower ATP levels.^[60]

6. An emerging paradigm: the Energy Maintenance Theory of Aging

We believe that available data suggests an emerging paradigm that we are referring to as the “Energy Maintenance Theory of Aging” (EMTA). The EMTA posits that long-lived individuals must maintain relatively abundant ATP levels in order to survive during extended longevity. Note that the energy maintenance is in the context of the general overall decrease in ATP levels during aging. Mutations or treatments that increase ATP levels would thus be beneficial for longevity, while reductions in ATP levels would be deleterious (Fig. 1).

The increase in ATP levels can take many forms, including altering mitochondrial morphology, upregulating oxidative phosphorylation, ensuring the survival of healthy mitochondria, or increasing the generation of ATP through other pathways such as glycolysis. A failure to maintain adequate ATP levels leads to cellular aging and organismal death. An extreme example of accelerated decreases in ATP levels during aging is *C. elegans*, for which the levels of ATP normally drop dramatically during aging (to 20% of the level in young adults).^[46] Even though wild-type *C. elegans* adults live only an average of two weeks, the cells in aging animals exhibit the hallmarks of cellular aging that are observed in decades-old humans, including sarcopenia.^[61] The EMTA model suggests that the rapid decrease in ATP levels in *C. elegans* directly contributes to the rapid cellular aging phenotypes.

One should keep in mind when comparing the EMTA to other theories of aging that the emphasis in the EMTA is not on the mechanism that extends longevity, but rather on the requirements for such old animals to survive during the extended longevity. Thus, in *C. elegans*, while mitochondrial fusion is important for longevity (and we propose that its main function is to generate adequate ATP), the increased fusion is not sufficient to promote extreme longevity. Thus, the EMTA is predominantly a theory for maintaining survival during longevity rather than the sole determinant of lifespan. It should also be kept in mind that metabolic rate is not necessarily a direct readout of the use of ATP to prevent aging. Hou has applied quantitative modeling coupled to experimental data to clarify that the lifespan outcome can depend on the type of process metabolic output is applied to.^[62, 63] In these models, predominantly shuttling metabolic output to biosynthesis, such as organismal development, precludes its use in bolstering repair processes that combat cellular aging.

Stable energy levels are likely to promote the survival of older animals by allowing energy-intensive cellular repair and homeostasis mechanisms. The most notable of these processes is proteostasis.^[64] Protein folding requires extensive ATP for chaperone and chaperonin functions. Proteins that are unable to fold properly are degraded through the ubiquitin-proteasome system (UPS). The vast majority of proteins in the cytoplasm and nucleoplasm are also degraded through the UPS; which is responsible for the degradation of at least 80% of all cellular proteins.^[65] ATP is required for the UPS at multiple steps. ATP is required to activate each ubiquitin, and at least four activated ubiquitin are required as a poly-ubiquitin degradation signal; AAA-ATPases use ATP to move substrates from the ubiquitin protein ligase (E3) to the proteasome, which then uses ATP to unfold proteins prior to their degradation.^[65] The degradation of a protein by the proteasome is surprisingly energy intensive. For example, the degradation of the 21.5 kDa DHFR protein by the proteasome

requires 50–80 ATP, while the degradation of the larger (but still relatively small) 38 kDa Sic1 protein requires 100–160 ATP.^[66] Thus proteostasis is very energy intensive. Aging animals have a marked reduction in total energy expenditure.^[47] This reduction in available energy negatively impacts proteostasis, and results in the accumulation of damaged proteins and protein aggregates that contribute to cellular and organismal aging.^[64] Other homeostasis mechanisms that require extensive energy include the replacement of damaged organelles and mitochondria that are removed by autophagy and mitophagy, with inhibition of these processes leading to shorter lifespans.^[14, 67] The role of damage to lipids in aging is becoming more recognized, and the pathways to repair and replace lipids also require energy.^[68] Thus, there is a compelling reason to maintain ATP levels as cells age to maintain cell integrity, which directly impacts the functioning of tissues and organs.

7. Compatibility of the EMTA with other theories of aging

There are several theories of aging that appear on the surface to contradict the EMTA, these include the ‘rate of living’ theory, longevity in response to caloric restriction (CR)/dietary restriction (DR), the mitochondrial free radical theory of aging (MFRTA), the uncoupling to survive model, and increased mitophagy linked to lifespan extension. Here we will address how the EMTA is compatible with each of these theories.

The rate of living theory (ROL) introduced over a century ago postulates that there is an inverse correlation between body mass and energy metabolism.^[69] The theory hypothesizes that larger animals with higher body mass and relatively lower energy metabolism live longer than smaller animals. The ROL theory uses inferences across species, classes, and branches of animals. However, it is possible that among these diverse animals, different regulatory mechanisms for aging are utilized or emphasized. Further, many exceptions have weakened the correlation. For example, naked-mole rats that live for 25 to 30 years have similar levels of energy metabolism as mice that live only 3–4 years.^[9] Birds have a metabolic rate up to twice as high as similarly-sized mammals, yet they live on average about 3 times as long as body mass-matched mammals.^[70] There is no inverse relationship between life span and mass-specific metabolic rates in mice or fruit flies.^[68] Larger dog breeds usually have shorter lifespan than smaller dogs despite smaller dogs having higher rates of energy metabolism.^[63] Species of garter snake with higher metabolism and ATP levels live longer than species that have lower metabolism.^[71] Finally, exercise has been shown to decrease cellular aging in many organisms, and in some cases extend lifespan, despite increasing energy metabolism (see section 5). In part because of these problems, the ROL has been largely supplanted by theories with more defined mechanisms for linking a reduction in energy expenditure or mitochondrial respiration to lifespan extension, including CR and the MFRTA ^[72].

CR was originally thought to function predominantly through a decrease in metabolism in response to reduced levels of food. This would suggest that a reduction in energy metabolism would be correlated with longevity. However, this has been challenged by multiple studies that have observed no alteration or only a slight reduction in metabolic rate in response to CR (see extensive references in ^[63] and ^[73]). Thus, CR does not generally lead to decreased metabolism during aging. Rather, in several studies, CR leads to increased

metabolism/respiration, particularly in older animals. In budding yeast, CR extends lifespan and increases aerobic respiration and ATP levels, with the increase in lifespan dependent on the increase in aerobic respiration and ATP levels.^[74] In *C. elegans*, CR is associated with increased mitochondrial fusion and respiration, elevated ATP levels in older adults, and lifespan extension.^[28, 31, 75] Similarly, growth of *C. elegans* in axenic media, which is a form of CR, increases oxidative respiration, elevates ATP levels in older adults, and extends lifespan.^[76] An analysis of gene transcription in mice skeletal muscle revealed that normal aging was associated with a marked decrease in the expression of genes involved in metabolism, while CR induced the upregulation of genes that promote metabolism.^[77] In mammals, CR induces mitochondrial biogenesis, and starvation induces mitochondrial fusion, both of which allow more efficient ATP production.^[78] Thus, the ability of CR to increase or stabilize energy metabolism in older animals is consistent with the EMTA.

The Mitochondria Free Radical Theory of Aging (MRFTA) described by Harman in 1956 posits that free radicals generated by mitochondria mediate aging by inducing cellular damage.^[70, 79] The MRFTA is based on the observation that mtDNA mutations and ROS production increase with age, while mitochondrial function and ROS-scavenging enzymes decrease with age.^[9] On the surface, one would think that increases in energy metabolism would increase the level of ROS to thereby increase cellular aging. This would be in opposition to the EMTA model for which ATP generation is a key component in preventing aging. The initial focus of the MRFTA was on antioxidants that would prevent cellular damage from free radicals. However, analysis of many organisms showed that antioxidants do not prevent aging.^[80] Instead, increasing levels of antioxidants positively correlate with aging in many organisms.^[80] Further, inactivation of superoxide dismutase in *C. elegans* insulin pathway mutants makes the animals susceptible to oxidative stress but does not affect lifespan.^[81] These findings were initially used as evidence against the MRFTA; however, it has been subsequently argued that the critical target of the free radicals is the mitochondria itself, particularly mtDNA.^[72] The current thinking is that antioxidants or enzymatic ROS scavengers are unable to prevent this localized targeting of mitochondria by free radicals that are generated within the mitochondria.^[72] The targeting of mitochondria by free radicals fits the EMTA because the degradation of mitochondrial function by free radicals would lead to a reduction in mitochondrial ATP generation, which is broadly observed in older animals and correlates with shorter animal survival.^[9]

We do note that fragmented mitochondria (resulting from fission) generally produce higher levels of ROS, and so a shift toward elongated mitochondria would reduce ROS levels.^[82] Therefore, the elongated mitochondria in multiple *C. elegans* longevity pathways may have lower levels of ROS that also contribute to the lifespan extension. However, the importance of reducing ROS to extend lifespan is complicated by the fact that increased levels of ROS have been shown to extend lifespan in *C. elegans*, in part through the activation of the UPR^{mt} pathway.^[83]

The Uncoupling-to-Survive model posits that partial uncoupling of mitochondria (which reduces ATP generation) allows animals to survive longer by reducing the production of free radicals.^[69] This theory appears to directly contradict the idea that increased or maintained ATP production leads to animal survival, as uncoupled mitochondria produce less ATP.

However, it should be kept in mind that the uncoupling to survive theory arose from Speakman's observations that mice with higher metabolic intensity live longer than mice with lower metabolic intensity.^[51] In the mice with higher metabolic intensity there was an increase in the level of mitochondrial uncoupling.^[51] The uncoupling of mitochondria therefore occurred in the context of higher overall metabolic intensity. Similarly, a study of different human muscle types found that muscles with higher respiratory rates and mild uncoupling maintained ATP levels more effectively during aging and had better longevity than muscles that had lower respiratory rates with well-coupled mitochondria.^[84] In mice, mild uncoupling leads to higher rates of respiration and increased lifespan;^[85] and similar results were observed in yeast.^[86]

A recent study showed that uncoupling reduces ATP levels transiently in human cells in culture, followed by a sustained increase in ATP levels.^[87] The uncoupling induced a 4-fold increase in glycolysis, suggesting a mechanism by which uncoupling can reduce ROS levels while maintaining energy homeostasis.^[87] Overexpression of uncoupling UCP proteins maintains ATP production and increases lifespan in *C. elegans*, *Drosophila*, mice, and humans.^[85, 88] Note that the linkage between uncoupling and lifespan/healthspan is in the context of increased metabolic intensity. It is possible that mild uncoupling promotes longevity by allowing a higher metabolic intensity while limiting ROS-induced cellular damage. Thus, the correlation between higher metabolic intensity (in the context of mild uncoupling) and longevity is compatible with the EMTA.

Mitophagy promotes mitochondrial function and energy homeostasis by inducing elimination of dysfunctional mitochondria^[89]. Impairment of mitophagy occurs with age and contributes to the accumulation of damaged mitochondria with mtDNA mutations.^[14] Increased mitophagy is protective for mitochondrial health and is associated with increased lifespan in *C. elegans*, *Drosophila*, mice, and humans.^[14] One might consider that reducing mitochondria numbers through mitophagy would reduce the overall level of energy metabolism. Instead, however, mitophagy has been shown in several species to be associated with increased ATP levels by allowing accumulation of healthy mitochondria that are more energy efficient. Inactivation of mitophagy reduces ATP levels and lifespan in yeasts and *Drosophila*.^[90] Chemical inducers of mitophagy increase lifespan in *C. elegans* and improve muscle function in rodent models while maintaining sufficient energy production.^[91] Notably, mitophagic clearance of mitochondria is an ATP-driven process.^[92] Therefore, insufficient ATP levels can inhibit mitophagy, which in turn further reduces ATP levels. This has led to the suggestion of a mitochondrial "death spiral" that can accelerate aging.^[93] Thus, efficient mitophagy is associated with increased or maintained ATP levels, which is compatible with the EMTA.

8. Conclusions

Adult *C. elegans* exhibit increased mitochondrial fragmentation as they age. An increase in mitochondrial fusion is associated with diverse longevity pathways and is required for the survival of older *C. elegans* animals in these pathways. Elongated mitochondria are generally more efficient in generating ATP. The observation that the *C. elegans vhl-1* mutant does not require an increase in mitochondrial fusion for longevity suggests that it can bypass

the requirement for the underlying benefits that arise from increased mitochondrial fusion. Notably, loss of mammalian VHL can bypass the requirement for mitochondrial ATP generation through the upregulation of genes that mediate alternative energy metabolism pathways. Thus, *vhl-1* mutants may be the exception that proves the rule by allowing increased energy metabolism independently of increasing mitochondrial fusion.

In many animal species, ATP levels decrease during aging. mtDNA mutations that reduce ATP levels shorten lifespan in mammals. Further, genetic diseases with accelerated aging are associated with lower levels of ATP, thus solidifying the linkage between longevity and adequate ATP levels. Overall, these research findings provide evidence for the emerging paradigm that the survival of older animals during extended longevity requires the maintenance of energy metabolism. We are referring to this as the energy maintenance theory of aging. The maintenance of energy during aging can provide energy for cellular repair and homeostasis mechanisms such as proteostasis, and mitophagy and mitochondrial biogenesis to replace damaged mitochondria, all of which are ATP-driven anti-aging processes. We provided evidence that indicates that the EMTA is compatible with other broad theories of aging. We consider the EMTA as an emerging paradigm, and it will be important for future research to test this theory in diverse animals through the experimental manipulation of energy levels during aging. Such research would determine the extent to which maintaining energy levels contributes to longevity across the animal kingdom.

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Figure 1.

The Energy Maintenance Theory of Aging (EMTA). Energy levels in animals broadly decrease during aging. Mechanisms that extend lifespan utilize different pathways to increase or maintain energy generation. In *C. elegans*, diverse longevity pathways increase mitochondrial fusion, as elongated mitochondria are more efficient at ATP synthesis than fragmented mitochondria. Mitophagy allows more efficient energy metabolism by removing damaged mitochondria. Mild uncoupling reduces ROS generation to allow increased rates of energy metabolism without excessive levels of damaging ROS. Caloric restriction promotes increased energy levels by increasing mitophagy, mitochondrial fusion, and increased expression of genes for glycolysis and other energy metabolism pathways. Mitochondrial biogenesis allows the generation of healthy mitochondria to promote energy metabolism. Inactivation of VHL (potentially through mild hypoxic conditions), increases the levels of HIF1A, which upregulates the expression of genes required for energy generation via glycolysis. The maintenance of energy generation in older animals allows energy-dependent repair and homeostatic mechanisms that reduce damage associated with cellular aging to increase lifespan. All of these pathways may not operate in every animal species. See text for details.

Table 1.

Increased ATP levels are associated with increased lifespan in *C. elegans*

Genetic manipulation or treatment	Comparison genotype	Genotype/ Treatment	Adult stage for ATP analysis (days)	Life span (% control)	ATP level (% control)
Insulin/IGF receptor lof mutant ^[93]	wild type	<i>daf-2(e1370)</i>	10	199	400
Insulin/IGF receptor lof mutant + prohibitin RNAi ^[93]	wild type	<i>daf-2(e1370); (phb-1 RNAi)</i>	10	151	800
Insulin/IGF receptor lof mutant with prohibitin RNAi ^[93]	wild type	<i>daf-2(e1370); (phb-1 RNAi)</i>	10	145	600
ETC complex III lof mutant with prohibitin RNAi ^[93]	wild type	<i>isp-1(qm150); (phb-1 RNAi)</i>	10	178	375
ETC complex I lof mutant with prohibitin RNAi ^[93]	wild type	<i>gas-1(itc2); (phb-1 RNAi)</i>	10	137	425
ETC complex I lof mutant ^[94]	wild type	<i>nuc-6(qm200)</i>	1	181	217
ETC complex I lof mutant with paraquat ^[94]	wild type	<i>nuc-6(qm200); 0.1mM paraquat</i>	1	193	133
ETC complex I lof mutant with N-Acetyl Cysteine (NAC) ^[94]	wild type	<i>nuc-6(qm200); 1mM NAC</i>	1	170	233
HIF1A lof mutant with malate ^[95]	<i>hif-1(it4)</i>	<i>hif-1(it4); 10mM malate</i>	4	125	118
ubiquinone biosynthesis lof mutant ^[96]	wild type	<i>clk-1(qm30)</i>	1	150	160
slow development mutant ^[96]	wild type	<i>clk-3(qm38)</i>	1	~150	120
slow development mutant ^[96]	wild type	<i>clk-5(qm152)</i>	1	149	140
slow development mutant ^[96]	wild type	<i>clk-6(qm158)</i>	1	204	250
slow development mutant ^[96]	wild type	<i>clk-10(qm169)</i>	1	144	200
wild type on diet of <i>L. gasseri</i> bacterial ^[97]	wild type fed <i>E. coli</i>	wild type fed <i>Lactobacillus gasseri</i>	10	136	183
Insulin/IGF receptor lof mutant ^[28,98]	wild type	<i>daf-2(e1370)</i>	2–12	~250	~150–250
Notch receptor lof mutant with lithium ^[99]	<i>glp-1(q244)</i>	<i>glp-1(q244); 10mM Lithium</i>	8	111	167
wild type with pyrophosphoride-a (PPa) ^[100]	wild type	50μM PPa	5	121	165
mAAA protease paraplegin RNAi ^[28]	wild type (control RNAi)	<i>(ppgn-1 RNAi)</i>	1	130	140
CRL ubiquitin ligase component RNAi ^[28]	wild type (control RNAi)	<i>(lin-23 RNAi)</i>	1	124	135
CRL ubiquitin ligase regulator lof mutant ^[28]	wild type	<i>cand-1(tm1683)</i>	1	127	165

lof: loss-of-function