Prospects & Overviews

The mystery of *C. elegans* aging: An emerging role for fat

Distant parallels between *C. elegans* aging and metabolic syndrome?

Daniel Ackerman and David Gems[*]

New *C. elegans* studies imply that lipases and lipid desaturases can mediate signaling effects on aging. But why might fat homeostasis be critical to aging? Could problems with fat handling compromise health in nematodes as they do in mammals? The study of signaling pathways that control longevity could provide the key to one of the great unsolved mysteries of biology: the mechanism of aging. But as our view of the regulatory pathways that control aging grows ever clearer, the nature of aging itself has, if anything, grown more obscure. In particular, focused investigations of the oxidative damage theory have raised questions about an old assumption: that a fundamental cause of aging is accumulation of molecular damage. Could fat dyshomeostasis instead be critical?

Keywords:
- aging; autophagy; *C. elegans*; fat; hyperfunction; metabolic syndrome

Introduction

What is aging? Numerous pathways and interventions have now been discovered that can extend lifespan in model organisms, including dietary restriction and reduced insulin/IGF-1 signaling (IIS) [1]. Despite this, the biological mechanisms of the process of aging itself remain undiscovered. One plausible hypothesis is that organisms are no different from other complex structures, such as cars that wear out and break down or buildings that slowly corrode and crumble. Does wear and tear of the molecular structure of living systems cause our inevitable demise in a similar way?

One incarnation of this idea has it that reactive oxygen species (ROS) generated by mitochondrial respiration oxidize cellular constituents, resulting in aging [2]. But a number of recent studies have challenged the link between mitochondrial ROS generation, oxidative damage and longevity [3, 4]. Manipulations affecting oxidative stress levels have often yielded results that are not consistent with predictions of the theory. For example, interventions that increase oxidative stress in *Caenorhabditis elegans* can increase lifespan rather than reducing it [5–7]. In mice, recent carefully controlled studies of overexpression of antioxidant enzymes have not detected increases in lifespan [3]. This has lead to speculation that perhaps molecular damage is not the cause of aging after all [8–10].

Much research is currently focused on understanding the mechanisms operative in interventions that extend lifespan in short-lived model organisms such as the nematode *C. elegans* [1]. Yet given the cloud now hanging over the oxidative damage theory, this understanding has seemed more out of reach than ever. All this being so, there is particular interest in studies that identify associations between treatments that extend lifespan and biological processes that are not obviously connected to molecular damage. Here, we discuss a series of studies that point to a role of lipid status in longevity assurance in *C. elegans* [11–14], and wonder why triglyceride lipase and lipid desaturase activity might protect against aging.

Germline control of lipase levels and lifespan in *C. elegans*

Lipids serve as a major form of energy storage, the main component of cell membranes, and as signaling molecules. The new links between lipid biology and aging have largely emerged from studies of one particular treatment that extends lifespan in *C. elegans*: removal of the germline. This can be achieved either by laser ablation of gonad precursor cells or by genetic means [15, 16], and these interventions are thought to act by removing a germline-derived signal that promotes aging (Fig. 1). As in long-lived *C. elegans* mutants with reduced IIS, the effects of the germline on lifespan require the DAF-16 FoxO transcription factor [15]. But, as in IIS mutants, the biological processes downstream of DAF-16 that extend lifespan remain a mystery.

Here, new clues were provided in 2008 by work from the lab of Gary Ruvkun at Harvard University. They found that germline loss through mutation of the *glp-1* gene increases expression of the triglyceride lipase *lipl-4* and that this induction was required for full expression of longevity [17]. As in the case of lifespan extension, the increased lipase expression of germline mutants proved to require DAF-16. As DAF-16 activity is also increased in IIS mutants, the expression of *lipl-4* was tested in these mutants and was indeed elevated. As in germline mutants, *lipl-4* was required for full *daf-2* insulin/IGF-1 receptor mutant longevity while having no effect on lifespan in worms with wild-type IIS. Moreover, over-expression of *lipl-4* proved sufficient to extend lifespan [17].

Then, in 2009 it was found that deletion of the transcriptional co-repressor *ctbp-1* caused a DAF-16-dependent increase in both lifespan and expression of the lipase *lips-7* [18]. Again, loss of *lips-7* suppressed *ctbp-1* longevity but had no effect on lifespan in otherwise wild-type worms. Thus, three different modes of DAF-16-dependent longevity are mediated by increased lipase activity. This suggests that DAF-16-directed increases in lipolysis somehow slow aging.
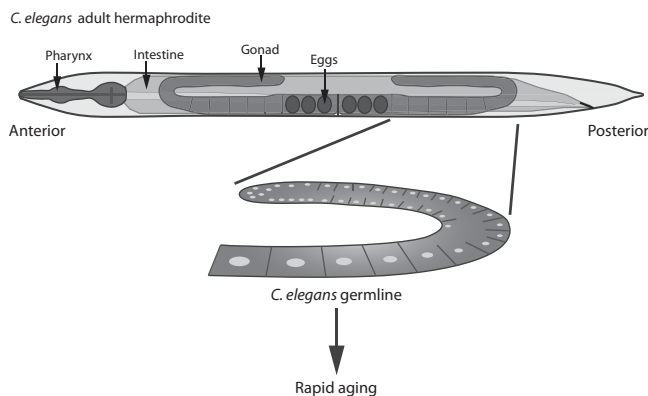

Figure 1. The nematode *C. elegans* is a popular model organism for aging research. Removal of the germline by any of several methods extends lifespan. This is thought to occur via a germline-derived signal that alters gene expression in the intestine via the transcription factor DAF-16.

Influence of the germline on target of rapamycin (TOR) and lipophagy

In 2011 several new studies elucidated further the link between longevity assurance and lipid biology in *C. elegans*. One, from the lab of Malene Hansen at the Sanford-Burnham Medical Research Institute at La Jolla, showed that changes in expression of the *lipl-4* lipase in germline mutants are triggered by reduced signaling by the nutrient sensor TOR [11]. TOR proved to control longevity through an interdependent regulation of autophagy and lipid homeostasis. Reduced TOR signaling has long been known to extend lifespan in a range of species [19], and the La Jolla study showed that germline removal reduces TOR (*let-363*) mRNA levels. The resulting longevity was dependent upon two downstream transcription factors: PHA-4 FoxA induced autophagy and DAF-16 FoxO induced lipase (*lipl-4*) expression (Fig. 2). Autophagy was previously
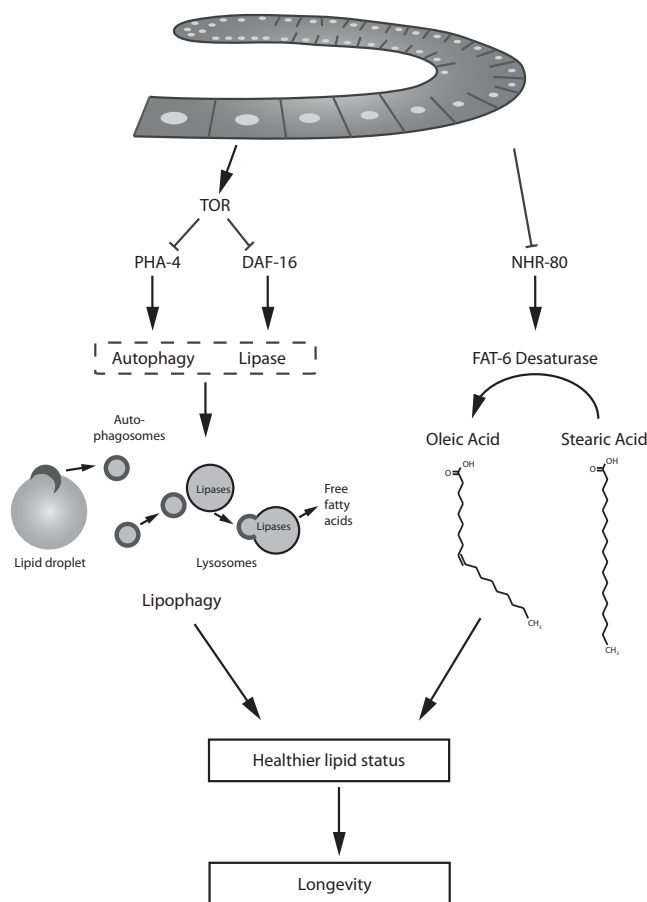

Figure 2. Several different mechanisms have been identified by which removal of the germline affects lipid metabolism in a manner that extends lifespan. First, loss of the germline causes a reduction in TOR expression, which induces lipase and autophagy expression via the two factors DAF-16 and PHA-4. In addition, germline loss also increases expression of the FAT-6 desaturase, which produces oleic acid from stearic acid. This suggests that germline loss induces a healthier lipid status, leading to increased longevity. How changes in lipid status affect longevity is unknown.

implicated in the extended lifespan resulting from reduced IIS or TOR signaling, or from dietary restriction [20–24].

Strikingly, autophagy proved necessary not only for *glp-1* mutant lifespan extension, but also for the elevated lipase activity. This harkens back to the response to starvation in mammalian hepatocytes, where breakdown of lipid droplets requires increased autophagy. Hepatocyte-specific inhibition of autophagy in mice led to an increased triglyceride and lipid droplet content after starvation compared to the autophagy-competent wild type [25].

Thus, autophagy and lipases can act together to mobilize lipids stored in lipid droplets – in a process now termed lipophagy. Lipid breakdown by the autophagy machinery occurs by partial engulfment of a lipid droplet by a penetrating membrane that seals on itself, creating an autophagosome that subsequently fuses with a lysosome (Fig. 2). Lysosomal lipases that work at low pH are then thought to break down lipids into free fatty acids (FFAs). The new study from the Hansen lab therefore suggests that germline mutants upregulate lipophagy, and that the resulting breakdown of lipid somehow leads to a deceleration of aging [11].

Fatty acid desaturases and longevity in *C. elegans*

Lipases are not the only kind of enzyme linked to fat metabolism that mediate germline effects on aging. It was recently found that germline-less mutants have elevated expression of the stearoyl-CoA-Δ9-desaturase (SCD) FAT-6 [12]. This enzyme desaturates the C18 fatty acid stearic acid to oleic acid (Fig. 2). Long-lived germline mutants have elevated oleic acid levels and a lower ratio of stearic acid to oleic acid. Loss of SCD activity reduces longevity in germline mutants, but not in wild-type worms. This is caused by reduced levels of oleic acid, since oleic acid supplementation can fully restore the longevity of SCD-deficient germline mutants.

Other fat metabolism genes may also be required for lifespan extension. For example transcriptome analysis of germline mutants detected altered expression of the predicted lipase gene *lips-17*, the fatty acid reductase *fard-1*, the fatty acid desaturase *fat-5* and the hydroxyacyl-CoA dehydrogenase *hacd-1* [14] (summarized in Table 1).

How does fat metabolism affect *C. elegans* lifespan?

The above studies suggest that alterations in the biology of fat contribute to retarded aging in germline, IIS and *ctbp-1* mutants. By what mechanisms might this occur? One possibility is that such alterations generate lipid signaling molecules that regulates lifespan [14]. In this scenario, altered lipid metabolism is not the long-sought ultimate determinant of aging rate, but rather yet another element of the regulatory network that modulates *C. elegans* lifespan. There are at least hints that this scenario is not the correct one. The *lips-7* lipase that is required for lifespan extension by *ctbp-1* knockout is clearly involved in determining gross levels of triacylglyceride storage. Loss of *lips-7* led to a 90% increase in total triacylglycerol (TAG) and long-lived *ctbp-1* mutants, which overexpress *lips-7*, had 17% less TAG than wild-type animals [18]. This suggests that gross changes in fat storage or composition may extend lifespan, rather than altered lipophilic signaling.

How else could changes in fat makeup extend lifespan? As ever, it is tempting to return to the fold of the oxidative damage theory of aging. For example, a shift in the composition of the fatty acid pool (e.g. less unsaturation) could make cellular membranes less susceptible to peroxidation [13]. This suggestion represents a variation of the old dogma, under which different rates of aging were thought to be achieved through changes in either ROS production or detoxification. Here, a shift in membrane composition would extend lifespan by increasing resistance to oxidative stress. Although logical, this model would have to be reconciled with data showing that increased levels of ROS are compatible with an extended lifespan [5, 9]. More biochemical studies of lipid peroxidation in long-lived mutants are needed to assess whether this is a plausible scenario.

One thing that is clear is that there is no simple correlation between overall fat content and lifespan. Worms under dietary restriction contain less fat, and both IIS mutants and germline deficient animals contain far more [26], and yet all are long lived. The evidence shows that the lifespan extension seen in germline mutants is achieved at least partially through increased lipase activity, but the overall elevation in fat levels in these mutants exclude a simple scenario in which lifespan is extended by making the worms leaner through increased lipophagy.

Table 1. Lipid metabolism genes implicated in *C. elegans* longevity

Gene name	Predicted function	Expression increased in:	Loss reduces lifespan of	
			Long lived mutant	Wild type
lipl-4	Lipase	Reduced IIS, germline mutant	IIS mutant, germline mutant	No
lips-7	Lipase	*ctbp-1* mutant	*ctbp-1* mutant	No
fat-6	Stearoyl-CoA-Δ9-desaturase	Germline mutant	Germline mutant[a]	No[a]
lips-17	Lipase	Germline mutant	Unknown	Unknown
fard-1	Fatty acid reductase	Germline mutant	Unknown	Unknown
fat-5	Fatty acid desaturase	Germline mutant	Unknown	Unknown
hacd-1	Hydroxyacyl-CoA dehydrogenase	Germline mutant	Unknown	Unknown

[a] Requires joint deletion of *fat-6* and *fat-7* to completely remove SCD activity.

Thus, these new studies seem to suggest that there exist healthy and unhealthy forms of lipid in *C. elegans*. Potentially, such variation in lipid status could involve changes in lipid composition, e.g. due to different levels of desaturation [12, 13], a shift toward shorter fatty acid chain lengths [13], or increased turnover due to high lipase expression.

Another possibility is that it is the subcellular and/or anatomical distribution of fat that affects aging rate. Indeed, a careful study of changes that occur during *C. elegans* aging found evidence of changing fat distribution in aged worms [27], with increased levels of lipid inclusions in muscle and hypodermis. In humans, the distribution of stored fat has major health consequences. Fat deposition in adipocytes is less harmful than in non-adipocytes [28] and subcutaneous fat is less harmful than visceral fat [29]. An interesting possibility is that altered fat metabolism in long-lived *C. elegans* prevents ectopic fat deposition in sites such as the musculature, thereby reducing lipotoxic effects.

Ectopic fat deposition and lipotoxicity as a cause of pathology

In humans, obesity commonly leads to metabolic syndrome, a complex of pathologies including type 2 diabetes, hypertension, and increased risk of cardiovascular disease. An emerging view is that the link between obesity and metabolic syndrome is not attributable simply to increased adipose tissue depots. Rather it is caused by the ectopic deposition of fat that occurs when the adipocyte fat storage capacity is exceeded, and which causes lipotoxic effects [28, 30, 31]. For example, increased plasma FFA levels cause intramyocellular and hepatocyte lipid accumulation, which contributes to insulin resistance and type 2 diabetes [32, 33]. Mouse models of ectopic fat deposition have provided evidence that fat deposition in non-adipocyte tissues can cause severe problems. For example, several models with genetic alterations causing increased fat deposition within heart muscle cells show that this can lead to myocardial dysfunction [34–36].

Thus, perhaps the ectopic accumulation of fat (e.g. beyond the intestine, gonad, and hypodermis) in elderly *C. elegans* [27] causes lipotoxic effects, contributing to the age-related decline in tissue function. One possibility is that FFAs themselves, or their metabolites, are responsible via effects on signal transduction pathways [37–40] or via effects on mitochondrial membrane permeability and cytochrome C release [41, 42]. A third possibility is that excess FFAs may cause oxidative stress, which damages cellular function [43].

A potential example of detrimental ectopic fat deposition in *C. elegans* is the redistribution of yolk lipoprotein after the cessation of reproduction. Yolk is present in *C. elegans* in the form of 12S and 8S lipoprotein particles, which contain high levels of lipids [44] and also transport cholesterol [45]. The protein component of yolk (vitellogenin) is encoded by five genes, *vit-2* to *vit-6*, which show sequence similarity to mammalian apolipoprotein B (*apoB*). Comparisons have been drawn previously between yolk particles and mammalian *apoB*-dependent low-density lipoprotein (LDL) [46, 47]. In mammals, LDL particles contribute to atherosclerosis,

suggesting distant parallels between the pathology of aging in worms and cardiovascular pathology in mammals.

In *C. elegans* yolk is synthesized in the intestine, and then transported across the body cavity (pseudocoelom) to the gonad, where it provisions developing oocytes [48]. After reproduction, yolk levels soar, and localization is no longer restricted to the intestine and oocytes but instead extends throughout the organism, particularly within the body cavity [27, 49, 50]. Such ectopic yolk deposition in old age could contribute to loss of tissue function. In fact, RNAi-mediated loss of expression of *vit-2* or *vit-5* increases *C. elegans* lifespan [51], and yolk protein levels are reduced in post-reproductive adults of the long-lived *daf-2* insulin/IGF-1 receptor mutant [52]. Thus, yolk accumulation may be pathological in *C. elegans*, perhaps reflecting ectopic fat deposition and lipotoxicity.

The cause of aging: Molecular damage or hyperfunction?

When viewed through the lens of the oxidative stress theory, aging is caused by the slow accumulation of oxidative damage and is therefore the inevitable consequence of metabolism. A different possibility has recently been proposed [8]: that aging is caused by *hyperfunction*, or the continuation of developmental processes (e.g. biosynthesis) in later life, with harmful effects (e.g. hypertrophy). This theory is consistent with the observation that pathways that influence aging often control the rate of growth and biosynthesis during development and reproduction [8]. According to this alternative model, aging is an unfortunate byproduct of regulatory systems that have been optimized by evolution for youthful growth and reproduction, and whose quasi-programmed, non-optimal, continued activity in later life leads to pathology and death (aging).

Ectopic yolk deposition in post-reproductive *C. elegans* is a potential example of quasi-programmed aging [8]. *C. elegans* biology is not optimized by evolution to produce yolk in a manner that would maximize longevity, but rather to assure that oocytes are provisioned in a way that maximizes reproductive success. The lack of selective pressure on post-reproductive traits precludes the evolution of a brake on yolk production to prevent its accumulation to deleterious levels. This scenario exemplifies a ''faucet left on'' mechanism of aging [27, 53]: if turning the faucet on is a program for drawing a bath, it can become a quasi-program for flooding the bathroom [8]. A similar relationship between growth and longevity might explain how shifts in fat composition in response to signals from TOR can affect lifespan.

Conclusions

The flurry of recent discoveries on the role of fat metabolism in lifespan determination has opened an exciting new path that might lead to a better understanding of aging. How alterations in lipid biology affect aging rate remain unclear. In this review, we have considered a number of hypotheses, which remain to be tested. The possibility that increased lipase extends lifespan simply by making worms leaner seems unlikely since long-lived germlineless and IIS mutants have
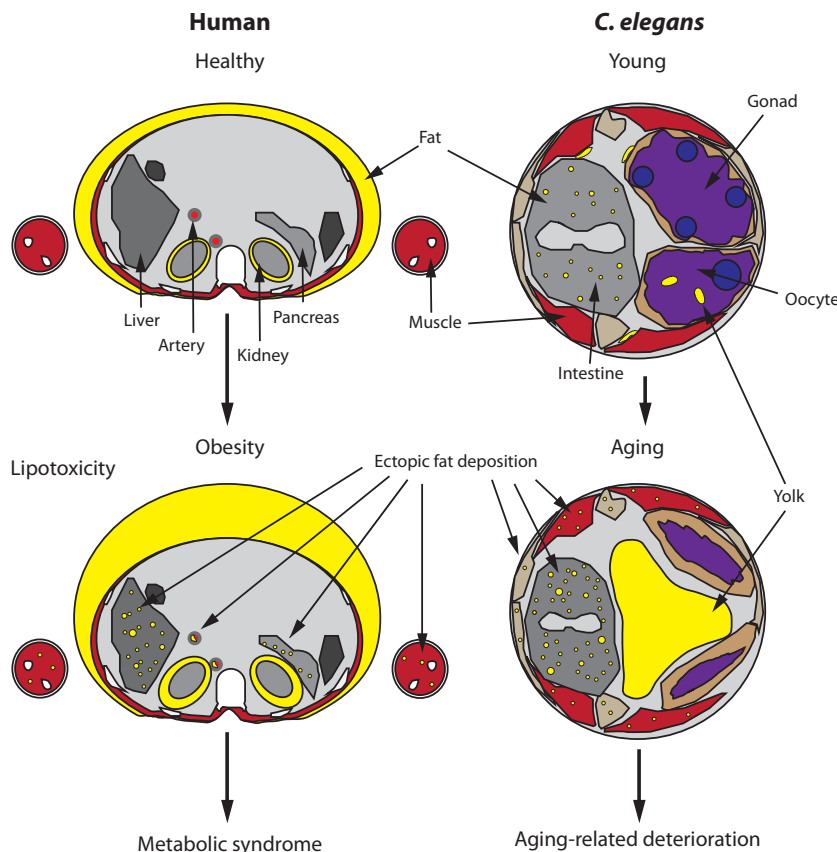
Figure 3. Possible parallels between metabolic syndrome in mammals, and lipid effects on aging in *C. elegans*. The role of lipid in worm aging as presented is a speculative model. Aging worms show a widespread increase in deposition of fat, and increased levels of yolk lipoproteins. Ectopic fat deposition appears to cause metabolic syndrome in humans, due to lipotoxicity. Here, we suggest that increased lipotoxicity through ectopic fat and yolk deposition might similarly contribute to the pathology of aging in *C. elegans*. Color code: dark gray, intestine (nematode) or liver (mammal); dark red, muscle; purple, gonad; yellow, lipid and lipoprotein.

more, not less, fat. Similarly, long-lived mouse mutants are sometimes lean (e.g. *S6K1*) [54] and sometimes fat (e.g. growth hormone deficient mutants) [55]. The major role for stearoyl-CoA-desaturase activity also suggests that it is changes in lipid composition, not total lipid levels, that retard aging.

Whatever the ultimate causes, it seems likely that signaling pathways downstream of the germline cause a shift to a more unhealthy lipid status. This is reminiscent of the situation in humans where for example, fat storage in adipose is healthier than in other tissues. As in humans, where lipid storage can lead to lipotoxicity and may be a cause of metabolic syndrome, ectopic fat deposition in aging worms may also affect longevity (Fig. 3). Several other hypotheses have been presented here, and the true role of fat metabolism in determining the rate of aging remains to be established. More research on *C. elegans* lipids is required to better understand how lipid status affects health and aging. This would be aided by improved techniques for visualizing lipid distribution in vivo, and tissue and subcellular variation in lipid composition.

Acknowledgments

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