Feature Review

Linking Lipid Metabolism to Chromatin Regulation in Aging

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The lifespan of an organism is strongly influenced by environmental factors (including diet) and by internal factors (notably reproductive status). Lipid metabolism is critical for adaptation to external conditions or reproduction. Interestingly, specific lipid profiles are associated with longevity, and increased uptake of certain lipids extends longevity in *Caenorhabditis elegans* and ameliorates disease phenotypes in humans. How lipids impact longevity, and how lipid metabolism is regulated during aging, is just beginning to be unraveled. This review describes recent advances in the regulation and role of lipids in longevity, focusing on the interaction between lipid metabolism and chromatin states in aging and age-related diseases.

**Introduction**

To survive in the wild, organisms need to adapt to highly variable conditions, such as cycles of fast and famine, fluctuations in temperature, and changes in reproductive status. A central mechanism underlying this adaptation is lipid metabolism. Lipids serve as efficient energy storage in the form of triglycerides, thereby ensuring survival under harsh conditions or changes in reproductive status. In addition to storing energy, lipids have a wide range of functions that could also contribute to adaptation. For example, lipids serve as structural components of cellular membranes, ensuring barrier and organelle homeostasis. Lipids can also act as signaling molecules, for example in nuclear hormone receptor (NHR) activation, influencing many processes, including gene expression. Thus, key questions are: how does lipid metabolism impact the organism under various conditions? Is lipid metabolism important for the regulation of aging and longevity?

Lipid profiles change with age in worms, fruit flies, mice, and humans [1–5]. Consistent with the idea that lipids are important for the regulation of lifespan, lipid profiles are altered in many long-lived *Caenorhabditis elegans* and *Drosophila melanogaster* mutants [6]. Mounting evidence points to a strong link between lipid metabolism, lifespan regulation, and reproductive status [6]. Indeed, the generation of offspring requires energy, and lipids can be actively transported from the soma to the germline and the offspring in a variety of species [7–9]. Consistently, removal of the germline leads to fat accumulation and increased longevity in worms and mammals [6]. Thus, lipid metabolism could be a critical switch between somatic maintenance and reproduction.

How do changes in lipid levels, composition, and location impact lifespan? An exciting possibility is that changes in lipid metabolism could alter the regulation of physiological processes through changes in chromatin states. Chromatin modifications (histone and DNA) are key long-lasting mechanisms for the regulation of gene expression, including genes involved in cellular maintenance and longevity [10–12]. Consistent with a role in the aging process, many chromatin marks change during aging and altering chromatin modifiers can...

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**Highlights**

The membrane lipids PE and PC decrease with age, whereas triglycerides generally increase. During aging, the fatty acid composition of membrane lipids shifts towards an increased PUFA to MUFA ratio.

Long-lived organisms or mutants have a decreased PUFA to MUFA ratio or less unsaturated PUFAs, consistent with lower oxidation. Longevity interventions (e.g., dietary restriction) lower the triglyceride content in mice.

Supplementation of specific MUFAs and PUFAs extends the lifespan of worms and improves age-related phenotypes in mammalian cells.

Dietary lipids are used as a carbon source for histone acetylation and dietary short-chain fatty acids as a source for histone acetylation.

Metabolites such as SAM connect lipid metabolism to histone methylation.

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extend lifespan in invertebrate and vertebrate species [10–12]. Chromatin marks are linked to lipid metabolism. Transfer of chromatin marks requires metabolites shared by lipid metabolism pathways, including acetyl-CoA, S-adenosyl methionine (SAM), and even lipids themselves [13]. Reciprocally, chromatin modifications control the expression of genes involved in various aspects of lipid metabolism, including synthesis, degradation, and storage. Thus, a tantalizing possibility is that lipid metabolism could interact with chromatin modifications to regulate aging.

In this review, we highlight recent work showing the importance of lipid metabolism for the regulation of aging. We focus on the relationship between lipid metabolism and chromatin modifiers by reviewing recent findings identifying how chromatin modifiers influence lipid composition and, vice versa, how lipids affect chromatin marks. We discuss the importance of the connection between lipid metabolism and chromatin for longevity. Finally, we propose that targeting lipid metabolism, or even lipids themselves, could be a promising strategy for lifespan-extending interventions.

**Lipid Metabolism Changes During Aging and Impacts Longevity**

Lipids are crucial for a variety of biological processes, including aging and longevity. Lipids are a diverse class of molecules that comprise lipophilic molecules (e.g., free fatty acids), steroids, and complex lipids (e.g., triglycerides and phospholipids) (Figure 1), and a number of methods have been developed to assess lipid levels and composition (Box 1). Lipid classes are differentially affected by aging- and longevity-promoting interventions. In this section, we review the recent evidence that implicates lipid levels and composition in longevity in a variety of species.

**Lipid Levels and Composition Are Altered During Aging and in Long-Lived Organisms**

Aging is associated with increased fat storage and altered complex lipid profiles [14]. In humans and mice, plasma triglyceride levels and circulating lipid–protein complexes increase with age [14] (Table 1). In mice, the levels of the membrane phospholipids phosphatidylethanolamine (PE), phosphatidylcholine (PC), and sphingomyelin decrease in old liver and brain, perhaps reflecting a change in plasma membrane composition [15,16] (Table 1). One possibility is that membrane fluidity is altered by membrane composition changes. Membranes are more fluid when they contain a low PC:PE ratio, a high degree of fatty acid unsaturation, a low concentration of oxidized lipids, or a low cholesterol content [17]. During aging, membrane fluidity decreases in the brain, liver, and heart of rats [17]. Long-lived organisms (e.g., naked mole-rats) exhibit a specific phospholipid/fatty acid saturation profile [18], which may help maintain membrane fluidity. Furthermore, longevity-promoting interventions such as dietary restriction (DR) protect from the age-dependent decline in membrane fluidity in mice [19]. Thus, increased membrane fluidity may be a key component of longer lifespan.

The notion that membrane composition is central to longevity is supported by studies suggesting that membrane lipids, notably sphingolipids, are biomarkers of human aging [20]. Serum profiling of long-lived humans revealed an increase in specific sphingolipids [20]. In addition, several plasma sphingolipids and their metabolites are also increased in long-lived naked mole-rats compared with wild type mice [21]. Sphingolipids can be converted into sphingosine-1-phosphate (S1P) and ceramides, two bioactive lipids with opposing biological effects (Figure 1) [22]. Whereas S1P promotes cell proliferation and survival, ceramides promote apoptosis [22–24]. The balance between S1P and ceramides, termed the S1P/ceramide axis, modulates the aging process [22]. Age-related diseases, including Alzheimer’s disease and diabetes, are associated with low levels of S1P [25,26]. Consistently, ceramides accumulate in old worms and humans [27,28] (Table 1). In addition, a ceramide-rich diet shortens lifespan in C. elegans [28]. Conversely, worm mutants that lack the enzyme that synthesizes ceramides are long-lived.
Thus, a shift in membrane composition during aging could modulate lifespan via the S1P/ceramide axis.

Aging is accompanied not only by changes in lipid levels, but also by changes in the fatty acid composition of complex lipids, notably fatty acid desaturation [30]. The level of saturation of the
lipid chain confers specific chemical properties to lipids, including solubility and fluidity, which could in turn affect the status of membranes. Saturation also alters lipid susceptibility to oxidative damage. For example, polyunsaturated fatty acids (PUFAs), which contain multiple double bonds in their carbon chains, are more susceptible to oxidation than monounsaturated fatty acids (MUFAs) [31]. Oxidized lipids are particularly detrimental to cellular function because (i) they catalyze free radical chain reactions which can damage both lipids and proteins, (ii) they diffuse over large distances in membranes, (iii) they can have long-lasting effects, and (iv) they alter membrane properties, eventually leading to loss of organelle integrity [32]. A metric to characterize the susceptibility to oxidation is the peroxidizability index (PI), which correlates with the number of unsaturated bonds in lipids [30]. During aging, the PI of membrane phospholipids increases, with higher PUFAs to MUFA ratio in old flies and rat liver [30,33]. Conversely, the PI of phospholipids is lower in the heart of long-lived wild-derived mouse strains than in that of control mouse strains [34]. Long-lived naked mole-rats also have low levels of phospholipids with highly unsaturated PUFAs (e.g., docosahexaenoic acid) compared with mice [18]. This correlation between low PI and longevity seems to extend to many species. Indeed, a low PI in phospholipids is a predictor of longevity across 11 mammalian species [35]. Furthermore, offspring of long-lived individuals have high MUFA to PUFAs ratios in erythrocyte membrane lipids compared with controls [36]. Hence, elevated products of lipid peroxidation may lead to cumulative cell and tissue damage, and possibly accelerate aging.

Intriguingly, changes in lipid profile during aging are tissue specific. Mitochondrial lipids of old mouse brains show a decrease in PUFAs, a change normally associated with longevity [37]. By contrast, mitochondrial lipids of old mouse muscles exhibit increased triglycerides and decreased PEs [37] (Table 1), changes generally associated with aging [37]. These differential changes in organelle lipid profiles in various tissues during aging could reflect diverse tissue-specific functions and energy requirements or compensatory protective mechanisms.

<table>
<thead>
<tr>
<th>Lipid class</th>
<th>Organism</th>
<th>Tissue</th>
<th>Change with age</th>
<th>Refs</th>
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<td>Rat</td>
<td>Brain mitochondria, heart mitochondria</td>
<td>Decrease</td>
<td>[158]</td>
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<tr>
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<td>C. elegans, human</td>
<td>Whole worm</td>
<td>Increase</td>
<td>[27,28]</td>
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<td>Plasma</td>
<td>Increase</td>
<td>[161]</td>
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<tr>
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<td>C. elegans</td>
<td>Whole worm</td>
<td>Down after reproduction</td>
<td>[3]</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>Mouse, rat</td>
<td>Liver, brain</td>
<td>Decrease</td>
<td>[15,16]</td>
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<tr>
<td>Phosphatidylcholine</td>
<td>C. elegans</td>
<td>Whole worm</td>
<td>Decrease</td>
<td>[3]</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>Mouse, rat</td>
<td>Liver, brain, brain mitochondria</td>
<td>Decrease</td>
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<td>C. elegans</td>
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<td>Decrease</td>
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<td>Liver, brain</td>
<td>Decrease</td>
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<td>C. elegans</td>
<td>Whole worm</td>
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<td>Increase</td>
<td>[161]</td>
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<td>Increase</td>
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<td>Triglyceride</td>
<td>Mouse</td>
<td>Liver, mitochondria brain</td>
<td>Increase</td>
<td>[5,15,16]</td>
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Table 1. Lipid Changes Detected During Aging
Consistently, lipid species that are predictors of long lifespan, including specific triglycerides, differ across various tissues [38]. More investigation is needed to elucidate the dynamic lipid profiles of different cell types and organelles during aging.

**DR, Which Delays Aging, Remodels Lipid Profiles**

DR is a well-known strategy to delay aging and slow the onset of age-related phenotypes [39–42]. DR can reverse age-associated lipid changes in mice [5,43]. In mouse liver, the phospholipid PE decreases during aging, but this decrease is blunted when old animals are subjected to DR [43]. In addition, DR increases S1P levels and decreases ceramide levels, thereby ameliorating age-dependent changes in these lipids [44]. Finally, the accumulation of triglycerides during aging in mouse liver is blunted by DR [5,43]. Interventions that mimic aspects of DR, such as resveratrol, also decrease triglyceride content in mouse plasma [45] and zebrafish plasma [46]. The effect of DR on triglycerides is conserved across species. DR decreases triglyceride levels in C. elegans (Figure 2) and longevity induced by DR in *Drosophila* requires an intact machinery for triglyceride synthesis and breakdown [47–49]. It will be important to determine whether overall triglyceride levels or triglyceride composition play a functional role in lifespan extension by DR, and if other aspects of lipid metabolism are also involved in lifespan extension by DR.

**Known Longevity Signaling Pathways Affect Lipid Metabolism**

Signaling pathways that regulate longevity, such as the insulin pathway and the mTOR-autophagy pathway, also impact lipid metabolism. These longevity pathways mostly act by influencing the activity of transcription factors that in turn modulate enzymes involved in lipid metabolism.

**Insulin Signaling Pathway**

Deficiency in the insulin receptor DAF-2 extends lifespan in *C. elegans* by activating the transcription factor DAF-16/FOXO [50–52]. DAF-16/FOXO transcriptionally upregulates lipid metabolic enzymes, such as the fatty acid desaturase FAT-7 and the lysosomal lipase LIPL-4, that subsequently promote MUFA synthesis and lipid degradation processes [53,54]. Consistent with these transcriptional changes, lipid profiling of *daf-2* mutant worms shows increased MUFA/PUFA ratios and elevated triglycerides [55–58] (Figure 2). In fact, long-lived insulin pathway mutants exhibit triglycerides whose side chains are enriched in MUFAs [56]. In addition, inhibiting this switch to MUFAs reduced the longevity of *daf-2* mutant worms [53]. Thus, high concentrations of cellular triglycerides may not always be detrimental to longevity, for example when they are enriched in MUFAs or when they occur in tissues rather than blood. The transcriptional response that is responsible for the switch to MUFAs upon insulin signaling deficiency can be blunted by other types of lipids. Indeed, high cholesterol concentration abrogates lifespan extension induced by deficiency in the insulin pathway [59]. An unanswered question is whether high cholesterol concentrations prevent the switch to MUFAs and how triglyceride composition mediates the beneficial effect of insulin signaling on lifespan.

The concomitant regulation of lifespan and lipid metabolism by the insulin pathway is conserved in other species. Long-lived insulin pathway deficiency in *Drosophila* (e.g., *InR* and *chico*) also increases triglyceride storage [60,61], possibly by affecting FOXO activity [62]. The insulin signaling pathway also influences longevity and lipid metabolism in mammals [60]. Insulin lowers plasma fatty acid levels by promoting triglyceride uptake from the blood into the adipose tissue and increases triglyceride synthesis [63]. In mice, the heterozygote mutation of *Igflt1* extends lifespan [64] and a mutation of the insulin receptor in the adipose tissue is sufficient to extend lifespan [65]. However, in contrast to invertebrates, mice harboring a mutation of the
**Figure 2. Lipid Metabolism Is Targeted by Several Longevity Pathways.** Longevity pathways that target lipid metabolism in *Caenorhabditis elegans* and mouse. Activated transcription factors/activators are circled. Upper panel: longevity pathways other than germline depletion. Dietary restriction in mouse leads to global DNA methylation changes that inhibit SREBP1. DNA hypermethylation is found on the bodies of genes that are important for fatty acid elongation. Dietary-restricted mice show a decrease in triglyceride level and a shift towards shorter chain fatty acids. In *C. elegans*, dietary restriction by eat-2 mutation results in activation of the nuclear hormone receptors NHR-49/PPAR and NHR-62/HNF4. The eat-2 mutants show decreased triglyceride content. Depletion of insulin signaling via daf-2/InR mutation activates DAF-16/FOXO and the coactivator MDT-15/MED15. This leads to an increase in triglycerides and a higher MUFA to PUFAs ratio. Activation of autophagy by mTOR depletion activates multiple transcription factors (HLH-30/TFEB, SKN-1/NRF, DAF-16/FOXO, and PHA-4/FOXA). Depletion of the COMPASS H3K4me3 modifiers ash-2/set-2 in the germline activates the transcription factors/activators SREBP-1/SREBP and MDT-15/MED15 in the worm soma. H3K4me3 modifier deficient worms have increased triglycerides and a higher MUFA content. Lower panel: longevity signaling upon germline depletion induced by glp-1 mutation in *C. elegans*. Multiple transcription factors and regulators are activated in germline-deficient animals (NHR-49/PPAR, MDT-15/MED15, NHR-80/HNF4, DAF-16/FOXO, TCER-1/TCERG1, SKN-1/NRF, HLH-30/TFEB, and PHA-4/FOX). Germline-deficient animals show higher triglyceride content, an increase in

*Figure legend continued on the bottom of the next page.*
insulin receptor in the adipose tissue have reduced whole body triglycerides [65]. Thus, high levels of triglycerides may not be important for insulin-mediated longevity in certain contexts. It remains to be determined if triglyceride content in specific tissues is altered or if triglyceride fatty acid composition changes in insulin pathway mutants in mammals.

**mTOR-Autophagy Pathway**

Another longevity pathway that links lipid metabolism to lifespan is the mTOR-autophagy pathway. Inhibiting mTOR extends lifespan and induces autophagy [66]. mTOR regulates overall fat storage [66–68], and autophagy is required to maintain lipid homeostasis in many organisms, including *C. elegans* [69,70]. The mTOR-autophagy pathway influences longevity in large part by modulating transcription factors that in turn regulate lipid metabolism enzymes. For example, autophagy-mediated longevity requires the transcription factor HLH-30/TFEB, which contributes to lipid homeostasis by upregulating the expression of lysosomal lipases (*lipf-2/3/4/5*) [71] (Figure 2). Depletion of mTOR via RNAi increases the expression and activity of the lipase LIPL-4 in *C. elegans* [72]. Overexpression of LIPL-4 extends lifespan and promotes autophagy by activating the transcription factor PHA-4/FOXA [72].

Autophagy-mediated lifespan extension not only involves lipases but also lipid binding proteins called vitellogenins [73]. Vitellogenins bind complex lipids and transport them from the intestine to the gonad. Thus, vitellogenins may change intracellular lipid availability, thereby affecting longevity. While vitellogenins do not have exact orthologs in mammals, they share functional similarity with mammalian large lipid transfer modules such as apolipoprotein B [e.g., low-density lipoprotein (LDL)] [74]. Similar to worms, high levels of circulating LDL are detrimental to health and are associated with increased incidence of age-related diseases such as cardiovascular diseases [75]. In addition, LDL levels are also regulated by autophagy [75]. It would be interesting to test if increasing the autophagic flux results in beneficial mammalian lipoprotein abundance and if this improves age-related phenotypes.

**Chromatin Modifiers Impact Lifespan via MUFA Metabolism**

Chromatin modifiers impact lifespan in worms by regulating fatty acid desaturation. Depletion of H3K4me3 modifiers of the COMPASS complex (*ash-2, set-2, wdr-5*) in the germline of fertile animals extends lifespan [76]. Deficiency of H3K4me3 modifiers in the germline leads to the activation of the coactivator MDT-15 and the transcription factor SBP-1 in the intestine [77]. These transcriptional regulators in turn upregulate fatty acid desaturase *fat-7* expression [77–79]. Knockdown of *fat-7* abrogates the longevity effect of H3K4me3 modifier deficiency, and *FAT-7* overexpression is sufficient to extend lifespan [77]. Mass spectrometry-based studies on these long-lived worms showed a switch towards an enrichment of MUFAbs, notably oleic acid, palmitoleic acid, and cis-vaccenic acid [77]. The mammalian *FAT-7* ortholog, SCD1, also regulates fat storage and fatty acid profiles [80], and SCD1 overexpression attenuates reactive oxygen species levels in obese mice [81]. It will be interesting to test if fatty acid desaturases also extend lifespan in vertebrates.

**Germline Longevity Signaling Regulates Lipid Metabolism via a Network of Transcription Factors**

A key dissection of the importance of lipid metabolism for longevity has been done in germline-deficient animals. Germline deficiency, via laser ablation or by genetic mutations that prevent germ cell proliferation, extends lifespan in worms and flies [82,83]. Concurrently, germline

unsaturated fatty acids, and an increase in the MUFA derivative oleylethanolamide. Abbreviations: MUFAbs, monounsaturated fatty acids; NHR, nuclear hormone receptor; PUFAs, polyunsaturated fatty acids.
removal leads to a drastic remodeling of lipid fat metabolism, not only in *C. elegans* but also in mammals [6]. Multiple transcription factors mediate lifespan extension in germline-deficient *C. elegans*, including the nuclear receptors NHR-49/PPAR [84], NHR-80/HNF4 [85], and DAF-12/LXRα [86], the transcription factors SKN-1/NRF [87] and HLH-30/TFEB [70,88], the Forkhead transcription factors PHA-4/FOXa [72] and DAF-16/FOXO [82], as well as the transcription elongation regulator TCER-1/TCERG1 [89] (Figure 2).

NHRs are required for the longevity of germline-deficient *C. elegans* and directly regulate the expression of several lipid metabolism genes (Figure 2). For example, NHR-49 upregulates genes involved in mitochondrial β-oxidation of lipids [84,90,91]. NHR-49, together with the coactivator MDT-15, also increases the expression of fatty acid desaturases such as *fat-5* and *fat-7* that promote the synthesis of various MUFA s, including palmitoleic and oleic acid [78]. The transcription factor NHR-80 also upregulates fatty acid desaturase genes involved in MUFA synthesis [85]. The central role of nuclear receptors in lipid metabolism in nematodes might be conserved in mammals. For example, the nuclear receptor PPARα, an NHR-49 ortholog, upregulates the fatty acid desaturase SCD1 [92]. In mice, PPARα signaling improves intestinal stem cell activity by inducing fatty acid degradation during aging [93], and a small molecule agonist for PPARα mimics this effect [93]. However, whether PPAR activators also promote longevity in mammals remains to be further studied.

Another example of a nuclear receptor pathway targeting lipid metabolism in long-lived germ-line-deficient *C. elegans* is the DAF-12 steroid signaling pathway [86] (Figure 2). In contrast to NHR-49, which is activated by fatty acid signals [94,95], DAF-12 is activated by cholesterol derivatives such as dafachronic acid [86]. One prominent function of DAF-12, and cholesterol, is the regulation of correct reproductive development in *C. elegans* [86]. Worms cannot synthesize cholesterol and need to uptake it from their food. Still, cholesterol is abundant in the gonad because lipid binding proteins (vitellogenins) transport the cholesterol uptaken from food into oocytes [96]. DAF-12 and the cholesterol-derivative dafachronic acid modulate lipid metabolism [97]. For example, one of the downstream targets of DAF-12 is the fatty acyl reductase *fadr-1/far1*, which is essential for longevity in germline-deficient *C. elegans* [97] (Figure 2). In addition, DAF-12 promotes the fusion of lipid droplets via unknown lipophilic hormones [98]. It remains to be analyzed if this process is involved in germine-deficiency mediated longevity.

The regulation of longevity and fat metabolism by the DAF-12 steroid signaling pathway may be conserved in mammals. Indeed, the potential DAF-12 mammalian ortholog, Liver X Receptor alpha (LXRα), is also activated by cholesterol derivatives [99]. A single nucleotide polymorphism in the gene encoding LXRXα was found to correlate with human longevity and, surprisingly, with higher levels of serum triglycerides [100]. While high serum triglyceride levels normally correlate with rapid aging, it is possible that here, triglyceride composition or downstream processing is different, which could be essential for longevity. Future work is needed to determine if cholesterol derivatives influence triglyceride composition and if this is involved in aging.

Other types of transcription factors, such as the Forkhead transcription factor DAF-16/FOXO, also mediate longevity in response to germline depletion by targeting lipid metabolism [50]. DAF-16/FOXO regulates target genes involved in lipid metabolism, including the lysosomal lipase *lip-4* [53,101] (Figure 2). Furthermore, DAF-16/FOXO and the transcription elongation and splicing factor TCER-1/TCERG1 can activate lipogenesis via *dgat-2*, *acs-22*, and *mboa-2* [89]. These transcriptional changes result in increased triglycerides levels and increased unsaturated fatty acids in germline-deficient worms [89].
Together, these findings highlight the beneficial effect of lipid accumulation for longevity in germine-deficient worms. Without a functioning germine, lipids can be repartitioned in somatic tissues. An exciting possibility is that lipids retained in the soma, for example triglycerides enriched in MUFAs [84], could contribute to the maintenance of somatic cells during aging. Lipids could activate specific longevity pathways in the soma or directly lower the risk of oxidative damage in somatic tissues.

**Dietary Supplementation of Specific Fatty Acids Extends Lifespan**

Manipulating lipid metabolism by supplementation of different dietary fatty acids can extend lifespan in *C. elegans*. One mechanism by which dietary lipids influence lifespan is by activating a transcription factor network [87,95]. For example, supplementation of the PUFA ω-3 fatty acid α-linolenic acid (ALA) extends lifespan in *C. elegans* through regulation of the NHR-49/PPARα and the SKN-1/NRF transcription factors [95] (Figure 3). ALA directly binds to and activates NHR-49 [95]. ALA indirectly leads to SKN-1/NRF activation via its peroxidized or hydroxylated counterparts (oxylipins) such as 9(S)-HpOTrE [95]. Thus, specific PUFAs, as well as their oxidation products, specify bind to pro-longevity transcription factors to confer longevity in *C. elegans*. It is not known if the transcriptional response induced by a specific PUFA is unique and if it depends on a particular cell type. Indeed, the PUFAs eicosapentaenoic acid and docosahexaenoic acid protect from cardiovascular diseases [102], whereas PUFAs such as linoleic acid and arachidonic acid (AA) are able to increase proliferation in different stem cell systems [103].

Supplementation of PUFAs [e.g., ω-6 PUFAs AA and dihomo-γ-linolenic acid (DGLA)] activates autophagy, thereby promoting longevity in *C. elegans* [104] (Figure 3). Activating autophagy by supplementation of PUFAs is conserved in human epithelial cells [104]. In addition, supplementation of PUFAs (AA and DGLA) during development in *C. elegans* improves protein quality control mechanisms that are normally decreased during aging, resulting in fewer toxic protein aggregates [105]. These observations highlight a crosstalk between different hallmarks of aging, namely lipid metabolism and protein homeostasis. It will be interesting to test if the longevity-promoting mechanisms of PUFAs found in worms are conserved in vertebrates, and if they also promote a healthy proteome during aging.

Dietary supplementation of MUFAs can also extend lifespan in *C. elegans* [77] (Figure 3). The MUFA oleic acid rescues longevity in germine-deficient worms that lack the fatty acid desaturases fat-6 and fat-7 [85]. Oleic acid also restores longevity in worms with a dual deficiency in H3K4me3 modifiers and in fat-7 [77]. In wild type *C. elegans*, supplementation of the MUFAs oleic acid, palmitoleic acid, or cis-vaccenic acid is sufficient to extend lifespan [77]. The longevity effect of oleic acid on wild type worms was not observed in two other studies [85,106], which might be due to a lower concentration of oleic acid [85] or the use of triglyceride species instead of free fatty acids to deliver oleic acid [106]. Dietary MUFAs, which are present in nuts, olives, and avocados, protect from cardiovascular diseases [107] and rescue obese mice from insulin resistance [108]. Additionally, in mice, MUFAs protect from the inflammatory phenotype induced by the SFA palmitic acid [109]. However, studies in mammals also emphasize the importance of a carefully balanced oleic acid metabolism. In Alzheimer’s disease mouse models, triglyceride accumulation is detected in the neural stem cell niche, and this is associated with decreased neural stem cell proliferation [110]. Mass spectrometry analysis of the neural stem cell niche shows that these triglycerides are enriched in oleic acid [110]. Interestingly, infusion of the free fatty acid oleic acid into the brain ventricles of wild type mice is sufficient to induce lipid accumulation and to inhibit neural stem cell proliferation *in vivo*, similar to phenotypes observed in Alzheimer’s disease models [110]. Thus, strongly increasing oleic
Acid concentration might not be beneficial in all cells/tissues. Understanding the molecular mechanisms underlying longevity induced by MUFA supplementation, and determining whether those are conserved, will be essential to uncover how diet influences longevity and healthy aging.
Finally, oleylthanolamide (OEA), an ethanolamide derivative of oleic acid, can extend lifespan in C. elegans by a signaling cascade involving a lipid binding protein and several transcription factors [94]. OEA binds to the fatty acid binding protein LBP-8, which subsequently translocates to the nucleus and activates NHR-49 and NHR-80 [94] (Figure 3). OEA directly binds to and activates NHR-80 [94], though the mechanism of NHR-49 activation by OEA remains unknown [94]. Thus, lipids can prolong lifespan both by binding to lipid binding proteins and activating transcription. As mammalian PPARs can also be activated by OEA [111], it will be interesting to determine if derivatives of MUFAs influence aging in mammals by directly activating nuclear transcription factors.

**Lipid Metabolism Regulates Chromatin Modifications**

Do lipids impact lifespan in part by affecting chromatin marks? Specific chromatin marks change with age, and chromatin modifiers influence lifespan in a variety of species [10]. The interaction between chromatin and lipid metabolism could occur via the direct addition of fatty acids to chromatin [112], or indirectly by triggering signaling pathways that affect chromatin states [113].

**Lipids Directly Act on Histone Acetylation and Acylation**

Acetyl-CoA is a degradation product of fatty acid oxidation and a metabolite shared between many different energy pathways. Histone acetyltransferases use acetyl-CoA as a cofactor to add acetyl groups to lysine residues on histones. Acetylated histones are associated with open chromatin and active gene expression. While acetyl groups used for histone acetylation can be derived from glucose in mammalian cells [114] or acetate in yeast [115], a large amount of acetyl groups are in fact provided by fatty acid oxidation [116]. Indeed, fatty acids such as octanoate can provide up to 90% of the acetyl groups on histones in cell culture under glucose starvation [116] (Figure 4A). Thus, the origin of acetyl-CoA used for histone acetylation may depend on both the organism and nutrient availability. An open question is how do cells sense the availability of acetyl-CoA to modify their chromatin profiles accordingly. Old cells may adapt their histone acetylation profile differently compared with young cells, particularly in response to environmental stress, such as starvation.

Short-chain fatty acids are also involved in a related histone modification: histone acylation. Histone acylation is similar to acetylation in that it is an activating chromatin mark that is added to a lysine residue. However, it differs in carbon chain length (>2 for acylation versus exactly 2 for acetylation) and charge (acylation neutralizes the positive charge of histones and can add further negative charge to histones, whereas acetylation only neutralizes the positive charge of histones) [117]. Butyrilation and crotonylation are other examples of acyl-modifications added to histones [117]. Isotope labeling of human cell lines with the short-chain fatty acids crotonate leads to the labeling of histone molecules, pointing to a direct addition of short-chain fatty acids to histones for acylation [112] (Figure 4A). In addition, short-chain fatty acids derived from the microbiota promote crotonylation at lysine 18 on histone H3 (H3K18) in mouse intestinal epithelial cells [118] (Figure 4A). In conclusion, dietary lipids are used indirectly via degradation and acetylation and directly via acylation to modify histone acetylation/acetylation marks. It will be interesting to understand how these chromatin marks are influenced during aging and if changes in lipid profiles during aging and longevity can account for chromatin profile changes.

**Lipid Metabolism and Histone Methylation Share Key Cofactors**

The interaction between lipid metabolism and chromatin also occurs because some lipids (phospholipids) and chromatin modifications share common precursors such as SAM [119]. SAM acts as a universal methyl donor for all cellular methylation reactions: lipid methylation,
Histone acetylation/acylation

(A) Short chain fatty acids
- Octanoate
- Crotonate/butyrate
- Acetyl-CoA
- Crotonyl-CoA
Fatty acid metabolism

(B) Methylation reactions
- SAM
- Histone methylation
- Phospholipid synthesis
- DNA methylation
- Phosphatidyl-choline
- Phosphatidyl-ethanolamine

Figure 4. Lipid Metabolism Interacts with Multiple Chromatin Modifications. (A) Dietary lipids are directly incorporated into histone acyl/acyl marks. Modified lysines (grey) are shown with the corresponding acetyl mark (pink) and acyl mark (yellow). Short-chain fatty acids (octanoate) can provide up to 90% of the acetyl groups on histones in cell culture under glucose starvation. Dietary short-chain fatty acids (crotonate) provide histone acyl marks in human cell lines [112]. Microbiota-derived short-chain fatty acids (butyrate) promote crotonylation at H3K18, H2BK5, and 19 additional lysines on H2A, H2B, H3, H4, and H1.2 in organoids of murine intestinal epithelial cells [118]. (B) The shared metabolite SAM connects lipid metabolism to epigenetic modifications. Modified lysines (grey) are shown with the corresponding methylation mark (blue). Phospholipid metabolism, and histone and DNA methylation share the common metabolite precursor SAM. Histones methylation, notably H3K4me3, H3K36me3, and H3K79me3, increases when phospholipid methylation is absent. It remains to be investigated if phospholipid metabolism also interacts with DNA methylation. Abbreviation: SAM, S-adenosyl methionine.

histone methylation, and DNA methylation. SAM is required for the methylation of PEs to generate PCs, which are the most abundant lipids in membranes [120]. Indeed, phospholipid methylation is the major consumer of cellular SAM in yeast [119]. Histone methylation is also dependent on the cellular concentration of SAM [121]. The enzyme that synthesizes SAM, S-methionine adenosyltransferase II (MATII), physically interacts with the histone methyltransferase SETDB1 in mouse cell lines. This interaction promotes H3K9 trimethylation at specific genomic loci [121]. Reducing the level of SAM by depleting MATII results in drastic histone methylation changes in cell culture, worms, and yeast [121–123]. Recent findings link lipid metabolism and histone methylation. Yeast cells lacking phospholipid methylation exhibit increased histone methylation on H3K4me3, H3K36me3, and H3K79me3, likely because more SAM is available for histone methylation when lipid methylation is defective (Figure 4B) [119]. Hence, lipid metabolism, notably phospholipid synthesis, may directly regulate histone marks by changing metabolite availability. It is also possible that phospholipid methylation affects DNA methylation via changes in SAM levels, although a direct connection between these processes has not yet been investigated. Of note, SAM concentrations change during aging [124] and reduction of SAM levels by DR of the SAM precursor methionine is beneficial for longevity in worms and mice [125]. Consistently, the concentration of the SAM
Box 1. Methods and Challenges in Studying Lipid Metabolism

Lipids participate in a variety of different cellular processes and many methods exist to assess lipid levels, composition, localization, and function. However, it is important to be aware of the limitations of different techniques. Staining: dyes (e.g., Oil Red O, Nile red) allow staining of neutral complex lipids such as triglycerides [163, 164]. Importantly, studies in C. elegans showed that fixation of samples is required to correctly assess the triglyceride content. In addition, fluorescence vital dyes such as BODIPY-labeled lipids can be used, especially in tissue culture setups, to analyze subcellular lipid distribution as well as membrane dynamics. These dyes help follow the localization of lipid molecules, although they do not inform on the exact lipid composition. Recent technical advances in mass spectrometry (MS) allow drastically improved sensitivity and accuracy in identification of novel lipid species and have uncovered quantitative lipid changes associated with aging and longevity. For example, gas chromatography followed by MS combined with derivatization, such as fatty acid methyl esterification, is ideal to assess cellular fatty acid profiles. In addition, liquid chromatography followed by MS enables detection of complex lipids, including their fatty acid composition. Limitations arise as MS methods do not allow single cell analysis or account for spatial resolution. To address this issue, microscopy methods coupled with MS such as desorption electrospray ionization-MS allow for the spatial analysis of lipid distribution in complex tissues such as the mammalian brain [165]. Excitingly, advances in stimulated Raman scattering (SRS) microscopy have made it possible to analyze subcellular lipid localization in a label-free manner in live cells [166, 167]. In addition, it is possible to use SRS to kinetically follow labeled fatty acids [166–168]. Of note, these microscopy methods require expensive and specialized equipment. To test the function of lipids, several methods have been developed. First, genetic manipulations or small molecule compounds can be used to delete/inhibit or activate enzymes involved in lipid metabolism. Lipid function can also be investigated by perturbing protein lipid binding partners. Many drugs approved for patients target lipid levels and thus lipid metabolism. Potential confounds for the use of drugs to study lipid metabolism are nonspecific off-target effects. Finally, free fatty acids can also be directly provided to animals via dietary supplementation or added to cells. However, lipids, especially at high concentration, could act nonspecifically by mass action [169]. In conclusion, many different methods exist to analyze lipids, and selecting the correct controls and experimental design is crucial to draw correct conclusions.

precursor methionine is significantly lower in the long-lived naked mole-rats compared with wild type mice [21, 126]. Thus, changes in SAM availability could play a central role during aging by affecting both lipid metabolism and histone/DNA methylation.

Lipid-Induced Signaling Pathways Indirectly Impact Chromatin States

Lipids provide precursors for inflammatory signaling, such as prostaglandins and lipopolysaccharide [127], which in turn can modulate chromatin states. Proinflammatory signals that derive from lipids are potent modifiers of epigenetic marks [128]. For example, proinflammatory lipopolysaccharides alter the H3K4me3 landscape in mouse primary bone macrophages [128]. Furthermore, the proinflammatory PUFA AA serves as a precursor for prostaglandins [127]. AA also induces DNA methylation via the activation of PPARα receptors in mammalian cell culture [113]. However, it remains unknown how precisely the epigenomic landscape is altered in response to these inflammatory signals. Human metabolic disorders, including obesity, are associated with global epigenomic changes, such as DNA methylation [129]. Future studies dissecting the underlying mechanism of lipid signaling on chromatin in inflammatory and metabolic disorders will help to understand long-lasting consequences of aberrant lipid signaling.

Lipids can also bind to transmembrane receptors, for example G protein-coupled receptors (GPCRs) [127], which can in turn induce a signaling cascade that impacts the epigenomic landscape. GPCRs are a large class of transmembrane receptors that react to extracellular ligands by activating intracellular signaling pathways [130]. Lipids interact with GPCRs (i) by modifying membrane properties, (ii) by acting as precursors for post-translational modifications of GPCRs, and (iii) by binding specifically into GPCR binding pockets [131]. A variety of lipids can bind GPCRs, including free fatty acids, their derivatives, phospholipid derivatives, and cholesterol [130]. For example, the GPCRs LPAR₁–₆ are activated by the phospholipid derivative lysophosphatidic acid (LPA) [132], and this can then influence the epigenomic landscape.
[133]. LPAR1 activation by LPA leads to recruitment of the histone deacetylase HDAC1 and the subsequent decrease in histone acetylation in human cancer cell lines [133]. Whether signaling cascades activated by LPA are involved in the regulation of aging remains to be determined. Other GPCR ligands play a central role in longevity-promoting interventions. S1P is an example of a lipid that binds to its GPCR receptors S1PR1-S with high affinity [134]. S1P levels decrease during aging and increase upon exercise and DR [22]. It will be interesting to determine how S1PR signaling influence aging and whether this involves remodeling of the epigenomic landscape.

**Chromatin Changes Drive Lipid Metabolism and Longevity**

Conversely, changes in chromatin modifications could impact fat metabolism and lifespan. The Sirtuin histone deacetylases are a good example of chromatin modifiers that link metabolism and aging, which has been reviewed extensively elsewhere [135–137]. Here we focus on recent advances of how chromatin modifications, notably histone and DNA methylation, influence lipid metabolism and longevity.

**Histone Methyltransferases Regulate Lipid Metabolism and Lifespan**

Histone methyltransferases have been recently discovered to link epigenetic modifications to lipid metabolism [77]. The COMPASS complex normally deposits methyl groups at H3K4 position, a histone mark associated with active transcription [138]. Deficiency in this H3K4me3 complex leads to lifespan extension in fertile C. elegans [76] (Figure 2) and can lead to lifespan extension in a transgenerational manner [139]. Knockdown of COMPASS H3K4me3 modifiers, such as set-2 and ash-2, specifically in the C. elegans germline, results in lifespan extension and an increase in triglycerides in the intestine of the worm [77]. Importantly, H3K4me3 complex deficiency leads to a change in fatty acid composition, with a switch to MUFAs by increasing fatty acid desaturase fat-7 expression. Inhibiting MUFA synthesis by fat-7 RNAi is sufficient to reduce lifespan extension and this can be rescued by dietary MUFAs [77]. These findings link deficiency in epigenetic modifiers in the germline to changes in intestinal fat metabolism, notably MUFAs, and lifespan extension in worms. It remains to be understood how MUFAs impact lifespan, and whether this also has transgenerational effects.

In flies, H3K4me3 modifiers also regulate lifespan [140]. However, it remains to be determined whether lipid accumulation is required for longevity in this context. In mammals, SET proteins, which regulate histone methylation, influence lipid metabolism [141,142]. For example, the H3K9 methyltransferase SETDB2 regulates lipid metabolism in mouse liver, in part by binding to the glucocorticoid receptor [141]. Upon fasting, the complex of SETDB2 and glucocorticoid receptor is recruited to the Insig2a promoter and upregulates the expression of Insig2a [141]. INSIG2A subsequently inhibits lipogenesis through SREBP inactivation in liver [141]. In this case, however, the methyltransferase SETDB2 acts by recruiting transcription factors rather than by globally modifying histones [141]. Another example of a SET protein regulating lipid metabolism is SETD1B. Depletion of the histone methyltransferase Setdb1 was found to cause aberrant lipid accumulation in female mice, which is associated with sterility [142]. This phenotype also seems to be independent of global H3K4 methylation changes [142]. Finally, a cytoplasmic complex between SET1B and the small kinetochore-associated protein BOD1 negatively regulates lipid accumulation in breast cancer cell lines, but with no global changes in H3K4me1 and H4K4me3 [143]. These observations highlight the role of SET-domain methyltransferases in lipid homeostasis, recruitment of transcription factors, and chromatin modification at specific genomic loci. Emerging evidence supports the notion that modulation of histone methylation at specific genomic loci influences lipid metabolism. Indeed, demethylation of H3K4me1 by LSD2 leads to the repression of specific genes involved in β-oxidation and lipid
transport, thereby suppressing fatty acid influx in mammalian liver [144]. Collectively, these studies raise the possibility that chromatin methylation modifiers affect local chromatin state at specific lipid metabolic genes by recruiting transcription factors. Whether these recruitment complexes change during aging remains to be examined.

**DNA Methylation Influences Lipid Metabolism**

DNA methylation may also play an important role in influencing lipid metabolism. This epigenetic mark occurs primarily at CpG dinucleotides and is generally associated with transcriptional repression [145]. DNA methylation patterns change with age in mice and humans [5,146,147]. While some studies report an overall decrease in global DNA methylation with age, others show an increase [5,146,147]. This observation suggests that the age-related remodeling of DNA methylation is specific to certain genomic loci.

Pro-longevity interventions, such as DR, delays age-related changes in DNA methylation profiles in mice and humans [5,148], and this appears to impact lipid metabolism. Notably, DR induces DNA hypermethylation on gene bodies, and these changes are associated with reduced expression of genes involved in lipid metabolism in mouse liver [5]. Consistently, DR induces the overall reduction in triglyceride levels and promotes enrichment in shorter chain fatty acids by reducing the expression of the fatty acid elongases Elovl5/6 [5]. Outstanding questions are whether DNA methylation at specific loci causally impacts lipid metabolism and whether these changes are critical for longevity by DR. More generally, could modifications to the diet, such as uptake of shorter chain fatty acids, provide the same benefits as DR on lifespan and health span?

**Concluding Remarks and Future Directions**

Lipids fulfill many cellular functions and their homeostasis is carefully maintained throughout life. Lipid imbalance occurs during aging and disease. To regulate lipid homeostasis and prevent imbalance, organisms need to sense and adapt to nutrient availability, and they often do so by modifying chromatin and gene expression. For example, dietary fatty acids directly impact histone acetylation and acylation [116,117]. In addition, common precursors are used for both membrane phospholipid synthesis and histone methylation [119], such that changes in lipid metabolism could generally impact chromatin states. There are several unanswered questions (see Outstanding Questions): for example, do age-dependent alterations in lipid composition account for changes in chromatin modifications during aging? Are age-induced chromatin modifications influenced by diet? Studies on how specific dietary lipids affect chromatin landscapes will likely shed new light into the mechanisms of lipid-regulated longevity.

Lipids play a critical role in adaptation to changes in environmental conditions. For example, lipid metabolism is particularly important during the circadian rhythm [149]. Liver lipid metabolism changes to adjust the lipogenesis/lipid breakdown to the energy requirements during day and night [149]. This adjustment is mediated at least in part by global gene expression changes via modification of the chromatin landscape. Indeed, oscillating chromatin landscapes during the circadian rhythm result in wide changes in gene expression, including genes involved in lipid metabolism [150]. It will be important to understand how the remodeling of lipid metabolism during the circadian rhythm impacts the aging process. Another environmental adaptation in which lipid metabolism plays a key role is exercise. Increased nutrient demands during exercise, or conversely, drastically reduced expenditure during “suspended animation”, for example hibernation in mammals, requires constant adjustment of cellular lipid metabolism [151,152]. It is interesting to note that these conditions coincide with changes to the chromatin landscape [153]. Understanding how lipid metabolism and chromatin remodeling intersect in

**Outstanding Questions**

- What are the key changes in lipid profiles during aging in different cell types?
- Is the remodeling of lipid profiles conserved in different species?
- How do altered lipid profiles regulate the aging process?
- Why are somatically retained lipids beneficial for longevity?
- Are changing lipid profiles during aging able to influence the epigenetic landscape, and is this conserved in different species?
- Can dietary interventions that focus on altered lipid/fatty acid intake reverse age-related changes in the epigenetic landscape?
- What are the effects of aberrant lipid regulation, for example due to high-fat diet, and of the resulting inflammation on the epigenome?
- Do other interventions that are beneficial for healthspan, including exercise, also change the epigenome by influencing lipid metabolism?
- How does reproductive status influence lipid metabolism and chromatin, and is it similar in females and males?
- Can lipids be used as ‘drugs’ to ameliorate age-related phenotypes or diseases in humans?
response to these stimuli will provide new insight into mechanisms of adaptation to extreme environmental conditions, and how these adaptations are altered during aging.

The reproductive status of an organism is essential for regulating lipid distribution. In worms, flies, and fish, lipid-rich yolk is packaged into eggs [154]. However, when lipids normally destined for the offspring are retained in somatic tissues, for example in the case of sterile animals, they appear to exert pro-longevity functions [5]. One possibility is that these specific lipids act as signals for longevity, perhaps by influencing the epigenomic landscape. In mammals, ovariectomy leads to increased somatic fat, which supports the link between changes in germline function and lipid metabolism [155]. Further studies will test whether and how these changes in lipid metabolism affect the chromatin landscape, and whether this plays a role in longevity.

Despite the link between lipid metabolism and chromatin, other nontranscriptional mechanisms of lipid metabolism could also influence cellular homeostasis and organismal lifespan. Indeed, many organelles that regulate lipid metabolism are central for cellular homeostasis. For example, lipid droplets, the storage organelle for lipids, buffer toxic lipid accumulation during autophagy and specifically protect mitochondria from lipotoxic deregulation [156]. In addition, the mitochondrial phospholipids cardiolipins mediate a mitochondria-to-cytosolic stress response [157]. During aging, mitochondrial cardiolipin decreases while oxidized cardiolipin species accumulate with age [158]. However, it remains to be investigated how these organelles, and their lipids, are regulated during aging and longevity. In addition peroxisomal proteins were found to be essential for lifespan extension by caloric restriction in yeast [159], highlighting an important role of the peroxisome, where lipids are catabolized, during aging. An open question is whether the specific lipids within lipid droplets, mitochondria, and peroxisomes are regulated during aging, and if these organelles play a functional role in regulating aging in various species.

Studies in worms and flies have provided invaluable insights into the role of lipids in lifespan, as well as the interactions between lipid and chromatin homeostasis. However, it is also important to note that invertebrate species do not have orthologs to all of the human genes involved in lipid regulatory mechanism. In addition, invertebrate models exhibit different reproductive traits, such as the production of a much larger brood size compared with mammals. Finally, in contrast to invertebrates, mammals possess specialized cell types, adipocytes, to store accumulated fat. Thus, several questions remain: are all the pro-longevity function of specific lipids and lipid-regulating pathways identified in invertebrates conserved in mammals? And could the different tissues or cells that store fat (e.g., liver, adipocytes) respond differently to lipid signals?

Lipids can have both beneficial and detrimental effects, depending on cell type or time, and understanding these differences could be particularly important for disease. For example, excessive storage of lipids is a risk factor for many diseases and circulating plasma lipids are associated with a higher risk for metabolic diseases [14]. In addition, specifically saturated fatty acids can deregulate intestinal stem cell proliferation, which leads to increased tumor occurrence [160]. Detailed knowledge on signaling cascades activated by fatty acids will shed light on the underlying mechanisms of the positive and negative effects of lipids. Despite numerous negative effects of lipids on human health, recent studies have highlighted an intriguing link between specific lipid profiles and longevity [14]. For example, in humans, there is a correlation between select phospholipid profiles and longevity [14]. Furthermore, increased lipid storage in triglycerides and free fatty acid signaling have both been shown to be associated with longevity.
[6]. However, we do not know which exact step of lipid regulation (increased storage of lipids, decreased degradation, or their downstream metabolic products) are most beneficial for longevity. One exciting possibility is that metabolic products of specific lipids activate pro-longevity transcription profiles, either by locally interacting with transcription factors or by globally impacting chromatin landscapes. Thus, lipids and their metabolites could be used as drug-like compounds to impact chromatin states and possibly aging. The ease of incorporating specific lipids to the diet could facilitate their delivery for therapeutic purposes. Knowledge of lipid metabolism, and its interaction with chromatin states, should offer innovative therapeutic strategies to counter aging and age-related diseases.

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References

5. Hahn, O. et al. (2017) Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. Genome Biol. 18, 56
Trends in Cell Biology

36. Puca, A.A. et al. (2009) Fatty acid profile of erythrocyte membranes as possible biomarker of longevity. Rejuvenation Res. 11, 63–72
44. Green, C.L. et al. (2017) The effects of graded levels of caloric restriction IX. Global metabolic screen reveals modulation of caminites, sphingolipids and bile acids in the liver of C57BL/6 mice. Aging Cell 16, 529–540
52. Lin, K. et al. (1997) dat-16: an HNF-3-like/keratin family member that can function to double the lifespan of Caenorhabditis elegans. Science 278, 1319–1322
69. Lapierre, L.R. et al. (2013) Autophagy genes are required for normal lipid levels in C. elegans. Autophagy 9, 278–286
77. Han, S. et al. (2017) Mono-unsaturated fatty acids link H3K4me3 modifiers to C. elegans lifespan. Nature 544, 186–190
Trends in Cell Biology


92. Paquette, A. et al. (2008) Effects of ovarioectomy on PPARα, SREBP-1c, and SCD-1 gene expression in the rat liver. Menopause 15, 1169–1175


104. O’Rourke, E.J. et al. (2013) ω-3 Polyunsaturated fatty acids extend life span through the activation of autophagy. Genes Dev. 27, 429–440


108. Oliveira, V. et al. (2013) Diets containing ω-3linoleic (ω3) or oleic (ω6) fatty acids rescues obese mice from insulin resistance. Endocrinology 156, 4033–4046


126. Ma, S. et al. (2015) Organization of the mammalian metabolome according to organ function, lineage specialization, and longevity. Cell Metab. 22, 332–343


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