Published in final edited form as:

Trends Cell Biol. 2019 February ; 29(2): 97–116. doi:10.1016/j.tcb.2018.09.004.

Linking lipid metabolism to chromatin regulation in aging

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Abstract

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 *C. 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 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 *C. elegans* and *D. 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,

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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 mechanism 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 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, 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). These 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 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 to 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 [29]. 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 PUFA 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. docosahexanoic acid) compared to 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 eleven mammalian species [35]. Furthermore, offspring of long-lived individuals have high MUFA to PUFA ratios in erythrocyte membrane lipids compared to 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]. In 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. 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.

Dietary restriction, which delays aging, remodels lipid profiles—Dietary restriction (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 *Igf1r* 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 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 (*lip1-2/3/4/5*) [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. 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 co-activator 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 MUFAs, 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 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/LXR α [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).

Nuclear hormone receptors (NHR) 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 co-activator MDT-15, also increases the expression of fatty acid desaturases such as *fat-5* and *fat-7* that promote the synthesis of various MUFAs, 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 PPAR α , a NHR-49 ortholog, upregulates the fatty acid desaturase SCD1 [92]. In mice, PPAR δ signaling improves intestinal stem cell activity by inducing fatty acid degradation during aging [93], and a small molecule agonist for PPAR5 mimics this effect [93]. However, whether PPAR activators also promote longevity in mammals remains to be further studied.

Another example of a nuclear receptor pathways targeting lipid metabolism in long-lived germline-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 *fard-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 germline-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 (LXR α), is also activated by cholesterol derivatives [99]. A single nucleotide polymorphism in the gene encoding LXR α 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 *lipf-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 germline-deficient worms. Without a functioning germline, lipids can be re-partitioned 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/PPAR α 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 oxidization products specifically 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 are able to increase proliferation in different stem cell systems [103].

Supplementation of PUFAs (e.g. ω -6 PUFAs arachidonic acid (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 germline-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, oleoylethanolamide (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 the nuclear hormone receptors NHR-49 and NHR-80 [94] (Figure 3). OEA directly binds to and activates the nuclear hormone receptor 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 to 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 vs. 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]. Butyrylation 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/acylation 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 S-adenosyl methionine (SAM) [119]. SAM acts as a universal methyl donor for all cellular methylation reactions - lipid methylation, 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 dietary restriction of the SAM precursor methionine is beneficial for longevity in worms and mice [125]. Consistently, the concentration of the SAM precursor methionine is significantly lower in the long-lived naked mole-rats compared to 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. Pro-inflammatory signals that derive from lipids are potent modifiers of epigenetic marks [128]. For example, pro-inflammatory lipopolysaccharides alter the H3K4me3 landscape in mouse primary bone macrophages [128]. Furthermore, the pro-inflammatory PUFA arachidonic acid serves as a precursor for prostaglandins [127].

Arachidonic acid also induces DNA methylation via the activation of PPAR α 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 inflammation 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 posttranslational 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 LPAR_{1–6} 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 S1PR₁₋₅ with high affinity [134]. S1P levels decrease during aging and increase upon exercise and DR [22]. It will be interesting to determine how S1 PR 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 *Setd1b* 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 at 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 dietary restriction (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: 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 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 [6]. One possibility is that these specific lipids act as signals for longevity, perhaps by influencing the epigenomic landscape. In mammals, ovariectomy leads to increase 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 non-transcriptional 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 to mammals [160]. 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 [161]. 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.

Text box 1

Methods and challenges 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 [164,165]. Importantly, studies in *C. elegans* showed that fixation of samples is required to correctly assess the triglyceride content [160]. 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 (DESI)-MS allow for the spatial analysis of lipid distribution in complex tissues such as the mammalian brain [166]. Excitingly, advances in *Stimulated Raman Scattering* (SRS) microscopy have made it possible to analyze sub-cellular lipid localization in a label-free manner in live cells [167,168]. In addition, it is possible to use SRS to kinetically follow labeled fatty acids [167–169]. 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 non-specific off-targets 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 non-specifically by mass action [170]. In conclusion, many different methods exist to analyze lipids, and selecting the correct controls and experimental design is crucial to draw correct conclusions.

Acknowledgments

Acknowledgements

We thank L. Booth, B. Demmitt, S. Han, S. Mahmoudi, R. Nath, and X. Zhao for helpful feedback on the manuscript. This work was supported by NIH R01AG054201 (A.B.) and the Deutsche Forschungsgemeinschaft (K. P.).

References

1. Houtkooper RH et al. (2011) The metabolic footprint of aging in mice. *Sci. Rep.* 1, 134 [PubMed: 22355651]
2. Lawton KA et al. (2008) Analysis of the adult human plasma metabolome. *Pharmacogenomics* 9, 383–97 [PubMed: 18384253]
3. Gao AW et al. (2017) A sensitive mass spectrometry platform identifies metabolic changes of life history traits in *C. elegans*. *Sci. Rep.* 7, 1–14 [PubMed: 28127051]
4. Moghadam NN et al. (2013) Age-induced perturbation in cell membrane phospholipid fatty acid profile of longevity-selected *Drosophila melanogaster* and corresponding control lines. *Exp. Gerontol.* 48, 1362–1368 [PubMed: 24012994]
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 [PubMed: 28351387]
6. Hansen M et al. (2013) Reproduction, fat metabolism, and life span: What is the connection? *Cell Metab.* 17, 10–19 [PubMed: 23312280]
7. Kimble J and Sharrock WJ (1983) Tissue-specific synthesis of yolk proteins in *Caenorhabditis elegans*. *Dev. Biol.* 96, 189–96 [PubMed: 6825952]
8. Yan Y-L and Postlethwait JH (1990) Vitellogenesis in *Drosophila*: Sequestration of a yolk polypeptide/invertase fusion protein into developing oocytes. *Dev. Biol.* 140, 281–290 [PubMed: 2115478]
9. Clelland E and Peng C (2009) Endocrine/paracrine control of zebrafish ovarian development. *Mol. Cell. Endocrinol.* 312, 42–52 [PubMed: 19406202]
10. Benayoun BA et al. (2015) Epigenetic regulation of ageing: linking environmental inputs to genomic stability. *Nat. Rev. Mol. Cell Biol.* 16, 593–610 [PubMed: 26373265]
11. Pal S and Tyler JK (2016) Epigenetics and aging. *Sci. Adv.* 2, e1600584 [PubMed: 27482540]

12. Sen P et al. (2016) Epigenetic Mechanisms of Longevity and Aging. *Cell* 166, 822–839 [PubMed: 27518561]
13. Berger SL and Sassone-Corsi P (2016) Metabolic signaling to chromatin. *Cold Spring Harb. Perspect. Biol.* 8, 1–24
14. Gonzalez-Covarrubias V (2013) Lipidomics in longevity and healthy aging. *Biogerontology* 14, 663–672 [PubMed: 23948799]
15. Braun F et al. (2016) Altered lipid metabolism in the aging kidney identified by three layered omic analysis. *Aging (Albany. NY)*. 8, 441–57 [PubMed: 26886165]
16. Lin L et al. (2016) In vivo HMRS and lipidomic profiling reveals comprehensive changes of hippocampal metabolism during aging in mice. *Biochem. Biophys. Res. Commun.* 470, 9–14 [PubMed: 26707637]
17. Hulbert AJ et al. (2007) Life and Death: Metabolic Rate, Membrane Composition, and Life Span of Animals. *Physiol. Rev.* 87, 1175–1213 [PubMed: 17928583]
18. Mitchell TW et al. (2007) Membrane phospholipid composition may contribute to exceptional longevity of the naked mole-rat (*Heterocephalus glaber*): A comparative study using shotgun lipidomics. *Exp. Gerontol.* 42, 1053–1062 [PubMed: 18029129]
19. Yu BP et al. (1992) Effect of age-related lipid peroxidation on membrane fluidity and phospholipase A2: modulation by dietary restriction. *Mech. Ageing Dev.* 65, 17–33 [PubMed: 1405788]
20. Montoliu I et al. (2014) Serum profiling of healthy aging identifies phospho- and sphingolipid species as markers of human longevity. *Aging (Albany. NY)*. 6, 9–25 [PubMed: 24457528]
21. Lewis KN et al. (2018) A window into extreme longevity; the circulating metabolomic signature of the naked mole-rat, a mammal that shows negligible senescence. *GeroScience* 40, 105–121 [PubMed: 29679203]
22. Green C et al. (2017) Energy balance and the sphingosine-1- phosphate/ceramide axis. *Aging (Albany. NY)*. 9, 1955–1956 [PubMed: 29017149]
23. Huang Y-L et al. (2014) Extrinsic sphingosine 1-phosphate activates S1P5 and induces autophagy through generating endoplasmic reticulum stress in human prostate cancer PC-3 cells. *Cell. Signal.* 26, 611–618 [PubMed: 24333325]
24. Chang C-L et al. (2009) S1P 5 is required for sphingosine 1 -phosphate- induced autophagy in human prostate cancer PC-3 cells. *Am. J. Physiol. Physiol.* 297, C451–C458
25. He X et al. (2010) Deregulation of sphingolipid metabolism in Alzheimer's disease. *Neurobiol. Aging* 31, 398–408 [PubMed: 18547682]
26. Spiegel S and Milstien S (2003) Sphingosine-1-phosphate: an enigmatic signalling lipid. *Nat. Rev. Mol. Cell Biol.* 4, 397–407 [PubMed: 12728273]
27. Huang X et al. (2014) Sphingolipids and lifespan regulation. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* 1841, 657–664
28. Cutler RG et al. (2014) Sphingolipid metabolism regulates development and lifespan in *Caenorhabditis elegans*. *Mech. Ageing Dev.* 143-144, 9–18 [PubMed: 25437839]
29. Jun H-J et al. (2012) Hepatic lipid accumulation alters global histone h3 lysine 9 and 4 trimethylation in the peroxisome proliferator-activated receptor alpha network. *PLoS One* 7, e44345 [PubMed: 22973438]
30. Pamplona R (2008) Membrane phospholipids, lipoxidative damage and molecular integrity: A causal role in aging and longevity. *Biochim. Biophys. Acta - Bioenerg.* 1777, 1249–1262
31. Bielski BH et al. (1983) A study of the reactivity of HO₂/O₂- with unsaturated fatty acids. *J. Biol. Chem.* 258, 4759–61 [PubMed: 6833274]
32. Hulbert AJ (2003) Life, death and membrane bilayers. *J. Exp. Biol.* 206, 2303–2311 [PubMed: 12796449]
33. Jeon TI et al. (2001) Effect of dietary restriction on age-related increase of liver susceptibility to peroxidation in rats. *Lipids* 36, 589–93 [PubMed: 11485162]
34. Hulbert AJ et al. (2006) Extended longevity of wild-derived mice is associated with peroxidation-resistant membranes. *Mech. Ageing Dev.* 127, 653–7 [PubMed: 16620917]

35. Jové M et al. (2013) Plasma long-chain free fatty acids predict mammalian longevity. *Sci. Rep.* 3, 3346 [PubMed: 24284984]
36. Puca AA et al. (2008) Fatty acid profile of erythrocyte membranes as possible biomarker of longevity. *Rejuvenation Res.* 11, 63–72 [PubMed: 18160025]
37. Pollard AK et al. (2017) Mouse mitochondrial lipid composition is defined by age in brain and muscle. *Aging (Albany, NY)*. 9, 986–998 [PubMed: 28325886]
38. Bozek K et al. (2017) Lipidome determinants of maximal lifespan in mammals. *Sci. Rep.* 7, 5 [PubMed: 28127055]
39. Fontana L and Partridge L (2015) Promoting health and longevity through diet: from model organisms to humans. *Cell* 161, 106–18 [PubMed: 25815989]
40. Anderson RM and Weindruch R (2010) Metabolic reprogramming, caloric restriction and aging. *Trends Endocrinol. Metab.* 21, 134–41 [PubMed: 20004110]
41. Fontana L et al. (2010) Extending Healthy Life Span--From Yeast to Humans. *Science (80-.)*. 328, 321–326
42. Mirzaei H et al. (2016) Dietary Interventions, Cardiovascular Aging, and Disease. *Circ. Res.* 118, 1612–1625 [PubMed: 27174953]
43. Jové M et al. (2014) Caloric restriction reveals a metabolomic and lipidomic signature in liver of male mice. *Aging Cell* 13, 828–837 [PubMed: 25052291]
44. Green CL et al. (2017) The effects of graded levels of calorie restriction: IX. Global metabolomic screen reveals modulation of carnitines, sphingolipids and bile acids in the liver of C57BL/6 mice. *Aging Cell* 16, 529–540 [PubMed: 28139067]
45. de Almeida Pinheiro T et al. (2017) Effects of Resveratrol and ACE Inhibitor Enalapril on Glucose and Lipid Profiles in Mice. *Protein Pept. Lett.* 24, 854–860 [PubMed: 28758594]
46. Ran G et al. (2017) Resveratrol ameliorates diet-induced dysregulation of lipid metabolism in zebrafish (*Danio rerio*). *PLoS One* 12, e0180865 [PubMed: 28686680]
47. Katewa SD et al. (2012) Intramyocellular fatty-acid metabolism plays a critical role in mediating responses to dietary restriction in *Drosophila melanogaster*. *Cell Metab.* 16, 97–103 [PubMed: 22768842]
48. Heestand BN et al. (2013) Dietary Restriction Induced Longevity Is Mediated by Nuclear Receptor NHR-62 in *Caenorhabditis elegans*. *PLoS Genet.* 9, e1003651 [PubMed: 23935515]
49. Roy-Bellavance C et al. (2017) The R148.3 Gene Modulates *Caenorhabditis elegans* Lifespan and Fat Metabolism. *G3 GenesGenomesGenetics* 7, 2739–2747
50. Ogg S et al. (1997) The Fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in *C. elegans*. *Nature* 389, 994–9 [PubMed: 9353126]
51. Kenyon C et al. (1993) A *C. elegans* mutant that lives twice as long as wild type. *Nature* 366, 461–464 [PubMed: 8247153]
52. Lin K et al. (1997) daf-16: An HNF-3/forkhead family member that can function to double the life-span of *Caenorhabditis elegans*. *Science* 278, 1319–22 [PubMed: 9360933]
53. Murphy CT et al. (2003) Genes that act downstream of DAF-16 to influence the lifespan of *Caenorhabditis elegans*. *Nature* 424, 277–83 [PubMed: 12845331]
54. Zhang P et al. (2013) Direct and indirect gene regulation by a life-extending foxo protein in *C. elegans*: Roles for GATA factors and lipid gene regulators. *Cell Metab.* 17, 85–100 [PubMed: 23312285]
55. Shmookler Reis RJ et al. (2011) Modulation of lipid biosynthesis contributes to stress resistance and longevity of *C. elegans* mutants. *Aging (Albany, NY)*. 3, 125–147 [PubMed: 21386131]
56. Castro C et al. (2013) A study of *Caenorhabditis elegans* DAF-2 mutants by metabolomics and differential correlation networks. *Mol. Biosyst.* 9, 1632 [PubMed: 23475189]
57. Prasain JK et al. (2015) Comparative Lipidomics of *Caenorhabditis elegans* Metabolic Disease Models by SWATH Non-Targeted Tandem Mass Spectrometry. *Metabolites* 5, 677–96 [PubMed: 26569325]
58. Perez CL and Van Gilst MR (2008) A ¹³C Isotope Labeling Strategy Reveals the Influence of Insulin Signaling on Lipogenesis in *C. elegans*. *Cell Metab.* 8, 266–274 [PubMed: 18762027]

59. Cheong MC et al. (2013) NSBP-1 mediates the effects of cholesterol on insulin/IGF-1 signaling in *Caenorhabditis elegans*. *Cell. Mol. Life Sci.* 70, 1623–1636 [PubMed: 23255046]
60. Gems D and Partridge L (2001) Insulin/IGF signalling and ageing: Seeing the bigger picture. *Curr. Opin. Genet. Dev.* 11, 287–292 [PubMed: 11377965]
61. Tatar M et al. (2001) A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science* 292, 107–110 [PubMed: 11292875]
62. Hwangbo DS et al. (2004) *Drosophila* dFOXO controls lifespan and regulates insulin signalling in brain and fat body. *Nature* 429, 562–566 [PubMed: 15175753]
63. Zhang J and Liu F (2014) Tissue-specific insulin signaling in the regulation of metabolism and aging. *IUBMB Life* 66, 485–495 [PubMed: 25087968]
64. Katic M and Kahn CR (2005) The role of insulin and IGF-1 signaling in longevity. *Cell. Mol. Life Sci.* 62, 320–343 [PubMed: 15723168]
65. Blüher M et al. (2003) Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science* 299, 572–4 [PubMed: 12543978]
66. Lamming DW and Sabatini DM (2013) A Central role for mTOR in lipid homeostasis. *Cell Metab.* 18, 465–9 [PubMed: 23973332]
67. Jones KT et al. (2009) Rictor/TORC2 Regulates *Caenorhabditis elegans* Fat Storage, Body Size, and Development through *sgk-1*. *PLoS Biol.* 7, e1000060
68. Soukas AA et al. (2009) Rictor/TORC2 regulates fat metabolism, feeding, growth, and life span in *Caenorhabditis elegans*. *Genes Dev.* 23, 496–511 [PubMed: 19240135]
69. Lapierre LR et al. (2013) Autophagy genes are required for normal lipid levels in *C. elegans*. *Autophagy* 9, 278–286 [PubMed: 23321914]
70. Lapierre LR et al. (2013) The TFEB orthologue HLH-30 regulates autophagy and modulates longevity in *Caenorhabditis elegans*. *Nat. Commun.* 4, 1–8
71. O'Rourke EJ and Ruvkun G (2013) MXL-3 and HLH-30 transcriptionally link lipolysis and autophagy to nutrient availability. *Nat. Cell Biol.* 15, 668–676 [PubMed: 23604316]
72. Lapierre LR et al. (2011) Autophagy and lipid metabolism coordinately modulate life span in germline-less *C. elegans*. *Curr. Biol.* 21, 1507–1514 [PubMed: 21906946]
73. Seah NE et al. (2016) Autophagy-mediated longevity is modulated by lipoprotein biogenesis. *Autophagy* 12, 261–272 [PubMed: 26671266]
74. Davis RA (1997) Evolution of Processes and Regulators of Lipoprotein Synthesis: From Birds to Mammals. *J. Nutr.* 127, 795S–800S [PubMed: 9164239]
75. Christian P et al. (2013) Autophagy: Emerging roles in lipid homeostasis and metabolic control. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* 1831, 819–824
76. Greer EL et al. (2010) Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in *C. elegans*. *Nature* 466, 383–387 [PubMed: 20555324]
77. Han S et al. (2017) Mono-unsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. *Nature* 544, 185–190 [PubMed: 28379943]
78. Taubert S et al. (2006) A Mediator subunit, MDT-15, integrates regulation of fatty acid metabolism by NHR-49-dependent and -independent pathways in *C. elegans*. *Genes Dev.* 20, 1137–49 [PubMed: 16651656]
79. Yang F et al. (2006) An ARC/Mediator subunit required for SREBP control of cholesterol and lipid homeostasis. *Nature* 442, 700–4 [PubMed: 16799563]
80. Sampath H and Ntambi JM (2014) Role of stearoyl-CoA desaturase-1 in skin integrity and whole body energy balance. *J. Biol. Chem.* 289, 2482–8 [PubMed: 24356954]
81. Matsui H et al. (2012) Stearoyl-CoA desaturase-1 (SCD1) augments saturated fatty acid-induced lipid accumulation and inhibits apoptosis in cardiac myocytes. *PLoS One* 7, e33283 [PubMed: 22413010]
82. Hsin H and Kenyon C (1999) Signals from the reproductive system regulate the lifespan of *C. elegans*. *Nature* 399, 362–6 [PubMed: 10360574]
83. Flatt T et al. (2008) *Drosophila* germ-line modulation of insulin signaling and lifespan. *Proc. Natl. Acad. Sci. U. S. A.* 105, 6368–73 [PubMed: 18434551]

84. Ratnappan R et al. (2014) Germline Signals Deploy NHR-49 to Modulate Fatty-Acid β -Oxidation and Desaturation in Somatic Tissues of *C. elegans*. *PLoS Genet.* 10,
85. Goudeau J et al. (2011) Fatty Acid Desaturation Links Germ Cell Loss to Longevity Through NHR-80/HNF4 in *C. elegans*. *PLoS Biol.* 9, e1000599 [PubMed: 21423649]
86. Antebi A (2013) Steroid regulation of *C. elegans* diapause, developmental timing, and longevity. *Curr. Top. Dev. Biol.* 105, 181–212 [PubMed: 23962843]
87. Steinbaugh MJ et al. (2015) Lipid-mediated regulation of SKN-1/Nrf in response to germ cell absence. *Elife* 4, 1–28
88. Nakamura S et al. (2016) Mondo complexes regulate TFEB via TOR inhibition to promote longevity in response to gonadal signals. *Nat. Commun.* 7,
89. Amrit FRG et al. (2016) DAF-16 and TCER-1 Facilitate Adaptation to Germline Loss by Restoring Lipid Homeostasis and Repressing Reproductive Physiology in *C. elegans*. *PLoS Genet.* 12,
90. Gilst MR Van et al. (2005) Nuclear Hormone Receptor NHR-49 Controls Fat Consumption and Fatty Acid Composition in *C. elegans*. *PLoS Biol.* 3, e53 [PubMed: 15719061]
91. Van Gilst MR et al. (2005) A *Caenorhabditis elegans* nutrient response system partially dependent on nuclear receptor NHR-49. *Proc. Natl. Acad. Sci. U. S. A.* 102, 13496–13501 [PubMed: 16157872]
92. Paquette A et al. (2008) Effects of ovariectomy on PPAR alpha, SREBP-1c, and SCD-1 gene expression in the rat liver. *Menopause* 15, 1169–75 [PubMed: 18665039]
93. Mihaylova MM et al. (2018) Fasting Activates Fatty Acid Oxidation to Enhance Intestinal Stem Cell Function during Homeostasis and Aging. *Cell Stem Cell* DOI: 10.1016/j.stem.2018.04.001
94. Folick A et al. (2015) Lysosomal signaling molecules regulate longevity in *Caenorhabditis elegans*. *Science* 347, 83–6 [PubMed: 25554789]
95. Qi W et al. (2017) The w-3 fatty acid α -linolenic acid extends *Caenorhabditis elegans* lifespan via NHR-49/PPAR α and oxidation to oxylipins. *Aging Cell* DOI: 10.1111/ace.12651
96. Matyash V et al. (2001) Distribution and Transport of Cholesterol in *Caenorhabditis elegans*. *Mol. Biol. Cell* 12, 1725–1736 [PubMed: 11408580]
97. McCormick M et al. (2012) New genes that extend *Caenorhabditis elegans*' lifespan in response to reproductive signals. *Aging Cell* 11, 192–202 [PubMed: 22081913]
98. Li S et al. (2017) Specific regulation of thermosensitive lipid droplet fusion by a nuclear hormone receptor pathway. *Proc. Natl. Acad. Sci.* DOI: 10.1073/pnas.1704277114
99. Lehmann JM et al. (1997) Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J. Biol. Chem.* 272, 3137–40 [PubMed: 9013544]
100. Mooijaart SP et al. (2007) Liver X receptor alpha associates with human life span. *J. Gerontol. A. Biol. Sci. Med. Sci.* 62, 343–9 [PubMed: 17452725]
101. Wang MC et al. (2008) Fat metabolism links germline stem cells and longevity in *C. elegans*. *Science* 322, 957–60 [PubMed: 18988854]
102. Tapiero H et al. (2002) Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. *Biomed. Pharmacother.* 56, 215–222 [PubMed: 12199620]
103. Kang JX et al. (2014) Concise Review: Regulation of Stem Cell Proliferation and Differentiation by Essential Fatty Acids and Their Metabolites. *Stem Cells* 32, 1092–1098 [PubMed: 24356924]
104. O'Rourke EJ et al. (2013) ω -6 Polyunsaturated fatty acids extend life span through the activation of autophagy. *Genes Dev.* 27, 429–40 [PubMed: 23392608]
105. Shemesh N et al. (2017) Dietary-Induced Signals That Activate the Gonadal Longevity Pathway during Development Regulate a Proteostasis Switch in *Caenorhabditis elegans* Adulthood. *Front. Mol. Neurosci.* 10, 1–14 [PubMed: 28167898]
106. Reisner K et al. (2010) Trans fat diet causes decreased brood size and shortened lifespan in *Caenorhabditis elegans* delta-6-desaturase mutant fat-3. *J. Biochem. Mol. Toxicol.* 25, 269–79
107. Gillingham LG et al. (2011) Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. *Lipids* 46, 209–28 [PubMed: 21308420]
108. Oliveira V et al. (2015) Diets containing α -linolenic (ω 3) or oleic (ω 9) fatty acids rescues obese mice from insulin resistance. *Endocrinology* 156, 4033–4046 [PubMed: 26280128]

109. Palomer X et al. (2018) Palmitic and Oleic Acid: The Yin and Yang of Fatty Acids in Type 2 Diabetes Mellitus. *Trends Endocrinol. Metab.* 29, 178–190 [PubMed: 29290500]
110. Hamilton LK et al. (2015) Aberrant Lipid Metabolism in the Forebrain Niche Suppresses Adult Neural Stem Cell Proliferation in an Animal Model of Alzheimer's Disease. *Cell Stem Cell* 17, 397–411 [PubMed: 26321199]
111. Fu J et al. (2003) Oleyethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR- α . *Nature* 425, 90–3 [PubMed: 12955147]
112. Tan M et al. (2011) Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. *Cell* 146, 1016–28 [PubMed: 21925322]
113. Silva-Martinez GA et al. (2016) Arachidonic and oleic acid exert distinct effects on the DNA methylome. *Epigenetics* 11, 321–334 [PubMed: 27088456]
114. Wellen KE et al. (2009) ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* 324, 1076–80 [PubMed: 19461003]
115. De Virgilio C et al. (1992) Cloning and disruption of a gene required for growth on acetate but not on ethanol: the acetyl-coenzyme A synthetase gene of *Saccharomyces cerevisiae*. *Yeast* 8, 1043–51 [PubMed: 1363452]
116. McDonnell E et al. (2016) Lipids Reprogram Metabolism to Become a Major Carbon Source for Histone Acetylation. *Cell Rep.* 17, 1463–1472 [PubMed: 27806287]
117. Sabari BR et al. (2017) Metabolic regulation of gene expression through histone acylations. *Nat. Rev. Mol. Cell Biol.* 18, 90–101 [PubMed: 27924077]
118. Fellows R et al. (2018) Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. *Nat. Commun.* 9, 105 [PubMed: 29317660]
119. Ye C et al. (2017) A Metabolic Function for Phospholipid and Histone Methylation. *Mol. Cell* 66, 180–193.e8 [PubMed: 28366644]
120. Bremer J and Greenberg DM (1961) Methyl transferring enzyme system of microsomes in the biosynthesis of lecithin (phosphatidylcholine). *Biochim. Biophys. Acta* 46, 205–216
121. Kera Y et al. (2013) Methionine adenosyltransferase II-dependent histone H3K9 methylation at the COX-2 gene locus. *J. Biol. Chem.* 288, 13592–601 [PubMed: 23539621]
122. Ding W et al. (2015) s-Adenosylmethionine Levels Govern Innate Immunity through Distinct Methylation-Dependent Pathways. *Cell Metab.* 22, 633–45 [PubMed: 26321661]
123. Li S et al. (2015) Serine and SAM Responsive Complex SESAME Regulates Histone Modification Crosstalk by Sensing Cellular Metabolism. *Mol. Cell* 60, 408–21 [PubMed: 26527276]
124. Stramentinoli G et al. (1977) Tissue levels of S-adenosylmethionine in aging rats. *J. Gerontol.* 32, 392–394 [PubMed: 864203]
125. Lee BC et al. (2016) Methionine restriction and life-span control. *Ann. N. Y. Acad. Sci.* 1363, 116–124 [PubMed: 26663138]
126. Ma S et al. (2015) Organization of the Mammalian Metabolome according to Organ Function, Lineage Specialization, and Longevity. *Cell Metab.* 22, 332–43 [PubMed: 26244935]
127. Wymann MP and Schneider R (2008) Lipid signalling in disease. *Nat. Rev. Mol. Cell Biol.* 9, 162–176 [PubMed: 18216772]
128. De Santa F et al. (2009) Jmjd3 contributes to the control of gene expression in LPS-activated macrophages. *EMBO J.* 28, 3341–3352 [PubMed: 19779457]
129. Cheng Z et al. (2018) Epigenetic reprogramming in metabolic disorders: nutritional factors and beyond. *J. Nutr. Biochem.* 54, 1–10 [PubMed: 29154162]
130. Im DS (2013) Intercellular lipid mediators and GPCR drug discovery. *Biomol. Ther.* 21, 411–422
131. Escriba PV et al. (2007) Lipid-protein interactions in GPCR-associated signaling. *Biochim. Biophys. Acta - Biomembr.* 1768, 836–852
132. Riaz A et al. (2016) G-protein-coupled lysophosphatidic acid receptors and their regulation of aKt signaling. *Int. J. Mol. Sci.* 17, 1–13
133. Ishdorj G et al. (2008) Lysophosphatidic acid protects cancer cells from histone deacetylase (HdAC) inhibitor-induced apoptosis through activation of HDAC. *J. Biol. Chem.* 283, 16818–16829 [PubMed: 18408217]

134. Rosen H et al. (2013) Sphingosine-1-Phosphate and Its Receptors: Structure, Signaling, and Influence. *Annu. Rev. Biochem.* 82, 637–662 [PubMed: 23527695]
135. Covington JD and Bajpeyi S (2016) The sirtuins: Markers of metabolic health. *Mol. Nutr. Food Res.* 60, 79–91 [PubMed: 26463981]
136. Cosentino C and Mostoslavsky R (2013) Metabolism, longevity and epigenetics. *Cell. Mol. Life Sci.* 70, 1525–1541 [PubMed: 23467663]
137. Houtkooper RH et al. (2012) Sirtuins as regulators of metabolism and healthspan. *Nat. Rev. Mol. Cell Biol.* 13, 225–238 [PubMed: 22395773]
138. Piunti A and Shilatifard A (2016) Epigenetic balance of gene expression by Polycomb and COMPASS families. *Science* 352, aad9780 [PubMed: 27257261]
139. Greer EL et al. (2011) Transgenerational epigenetic inheritance of longevity in *Caenorhabditis elegans*. *Nature* 479, 365–371 [PubMed: 22012258]
140. Li L et al. (2010) Essential functions of the histone demethylase Lid. *PLoS Genet.* 6,
141. Roqueta-Rivera M et al. (2016) SETDB2 Links Glucocorticoid to Lipid Metabolism through Insig2a Regulation. *Cell Metab.* 24, 474–484 [PubMed: 27568546]
142. Brici D et al. (2017) Setd1b, encoding a histone 3 lysine 4 methyltransferase, is a maternal effect gene required for the oogenic gene expression program. *Development* 144, 2606–2617 [PubMed: 28619824]
143. Wang L et al. (2017) A cytoplasmic COMPASS is necessary for cell survival and triple-negative breast cancer pathogenesis by regulating metabolism. DOI: 10.1101/gad.306092.117.
144. Nagaoka K et al. (2015) Lysine-specific demethylase 2 suppresses lipid influx and metabolism in hepatic cells. *Mol. Cell. Biol.* 35, 1068–80 [PubMed: 25624347]
145. Booth LN and Brunet A (2016) The Aging Epigenome. *Mol. Cell* 62, 728–744 [PubMed: 27259204]
146. Wilson VL and Jones PA (1983) DNA methylation decreases in aging but not in immortal cells. *Science* 220, 1055–7 [PubMed: 6844925]
147. Christensen BC et al. (2009) Aging and environmental exposures alter tissue- specific DNA methylation dependent upon CpG island context. *PLoS Genet.* 5, e1000602 [PubMed: 19680444]
148. Maegawa S et al. (2017) Caloric restriction delays age-related methylation drift. *Nat. Commun.* 8, 539 [PubMed: 28912502]
149. Gooley JJ (2016) Circadian regulation of lipid metabolism. *Proc. Nutr. Soc.* 75, 440–450 [PubMed: 27225642]
150. Feng D et al. (2011) A Circadian Rhythm Orchestrated by Histone Deacetylase 3 Controls Hepatic Lipid Metabolism. *Science* (80-.). 331, 1315–1319
151. Durstine JL et al. (2001) Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. *Sports Med.* 31, 1033–62 [PubMed: 11735685]
152. Carey H et al. (2003) Mammalian Hibernation: Cellular and Molecular Responses to Depressed Metabolism and Low Temperature. *Physiol. Rev.* 83, 1153–1181 [PubMed: 14506303]
153. McGee SL et al. (2009) Exercise-induced histone modifications in human skeletal muscle. *J. Physiol.* 587, 5951–5958 [PubMed: 19884317]
154. Byrne BM et al. (1989) The evolution of egg yolk proteins. *Prog. Biophys. Mol. Biol.* 53, 33–69 [PubMed: 2682782]
155. McElroy JF and Wade GN (1987) Short- and long-term effects of ovariectomy on food intake, body weight, carcass composition, and brown adipose tissue in rats. *Physiol. Behav.* 39, 361–5 [PubMed: 3575476]
156. Nguyen TB et al. (2017) DGAT1-Dependent Lipid Droplet Biogenesis Protects Mitochondrial Function during Starvation- Induced Autophagy. *Dev. Cell* 42, 1–13 [PubMed: 28697329]
157. Kim H et al. (2016) Lipid Biosynthesis Coordinates a Mitochondrial-to- Cytosolic Stress Response. *Cell* 166, 1539–1552.e16 [PubMed: 27610574]
158. Paradies G et al. (2010) Oxidative stress, mitochondrial bioenergetics, and cardiolipin in aging. *Free Radic. Biol. Med.* 48, 1286–1295 [PubMed: 20176101]
159. Anderson RM et al. (2003) Nicotinamide and PNC1 govern lifespan extension by calorie restriction in *Saccharomyces cerevisiae*. *Nature* 423, 181–185 [PubMed: 12736687]

160. Lemieux G.a and Ashrafi K (2014) Insights and challenges in using *C. elegans* for investigation of fat metabolism. *Crit. Rev. Biochem. Mol. Biol.* 9238, 1–16
161. Beyaz S et al. (2016) High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature* 531, 53–58 [PubMed: 26935695]
162. Greenfield MS et al. (1980) Effect of age on plasma triglyceride concentrations in man. *Metabolism*. 29, 1095–9 [PubMed: 7001176]
163. Schneeman BO and Richter D (1993) Changes in plasma and hepatic lipids, small intestinal histology and pancreatic enzyme activity due to aging and dietary fiber in rats. *J. Nutr.* 123, 1328–37 [PubMed: 7686573]
164. Mehlem A et al. (2013) Imaging of neutral lipids by oil red O for analyzing the metabolic status in health and disease. *Nat. Protoc.* 8, 1149–1154 [PubMed: 23702831]
165. Lemieux GA and Ashrafi K (2015) Insights and challenges in using *C. elegans* for investigation of fat metabolism. *Crit. Rev. Biochem. Mol. Biol.* 50, 69–84 [PubMed: 25228063]
166. Takats Z et al. (2004) Mass spectrometry sampling under ambient conditions with desorption electrospray ionization. *Science* 306, 471–3 [PubMed: 15486296]
167. Freudiger CW et al. (2008) Label-free biomedical imaging with high sensitivity by stimulated raman scattering microscopy. *Science* (80-.). 322, 1857–1861
168. Ramachandran PV et al. (2015) Label-free biomedical imaging of lipids by stimulated Raman scattering microscopy. *Curr. Protoc. Mol. Biol.* 109, 30.3.1–17
169. Yu Y et al. (2017) High-throughput screens using photo-highlighting discover BMP signaling in mitochondrial lipid oxidation. *Nat. Commun.* 8, 865 [PubMed: 29021566]
170. Smith NJ (2012) Low affinity GPCRs for metabolic intermediates: Challenges for pharmacologists. *Front. Endocrinol. (Lausanne)*. 3, 1–6

Outstanding questions box

1. What are the key changes in lipid profiles during aging in different cell types?
2. Is the remodeling of lipid profiles conserved in different species?
3. How do altered lipid profiles regulate the aging progress?
4. Why are somatically-retained lipids beneficial for longevity?
5. Are changing lipid profiles during aging able to influence the epigenetic landscape, and is this conserved in different species?
6. Can dietary interventions that focus on altered lipid/fatty acid intake reverse age-related changes in the epigenomic landscape?
7. What are the effects of aberrant lipid regulation, for example due to high fat diet, and of the resulting inflammation on the epigenome?
8. Do other interventions that are beneficial for healthspan, including exercise, also change the epigenome by influencing lipid metabolism?
9. How does reproductive status influence lipid metabolism and chromatin, and is it similar in females and males?
10. Can lipids be used as “drugs” to ameliorate age-related phenotypes or diseases in humans?

Highlights box

- 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 improve 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 acylation.
- Metabolites such as SAM connect lipid metabolism to histone methylation.

Figure 1. Lipid synthesis and degradation pathways

Fatty acids, including MUFAs and PUFAs, are synthesized and subsequently incorporated into triglycerides and phospholipids. Triglycerides are synthesized and stored in lipid droplets. Triglycerides can be degraded by two different mechanisms. Lysosomes can fuse with lipid droplets, and lysosomal lipases (LIPL1–5/LIPF) in turn can hydrolyze triglycerides during lipophagy, thereby releasing free fatty acids. Alternatively, lipases located directly at the lipid droplet interface such as the adipose tissue lipases (ATGL-1/ATGL1) hydrolyze triglycerides. Free fatty acids are degraded in mitochondria for energy generation. Peroxisomes degrade very long or branched fatty acids, which can be subsequently shuffled to mitochondria for further degradation. Membrane lipid synthesis pathways that are mentioned within the review are shown. SFAs: Saturated fatty acids, MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids, PC:

Phosphatidylcholine, PE: Phosphatidylethanolamine, PI: Phosphatidylinositol, PS: Phosphatidylserine, SIP: Sphingosine-1 -phosphate.

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Figure 2. Lipid metabolism is targeted by several longevity pathways

Longevity pathways that target lipid metabolism in *C. 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. *eat-2* mutants show decreased triglyceride content. Depletion of insulin signaling via *daf-2/InR* mutation activates DAF-16/FOXO and the co-activator MDT-15/MED15. This

leads to an increase in triglycerides and a higher MUFA to PUFA 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 SBP-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-12/LXR α , DAF-16/FOXO, TCER-1/TCERG1, SKN-1/NRF, HLH-30/TFEB, and PHA-4/FOXA,). Germline-deficient animals show higher triglyceride content, an increase in unsaturated fatty acids, and an increase in the MUFA derivative oleoylethanolamide (OEA). MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids, NHR: Nuclear hormone receptor.

Figure 3. Free fatty acid supplementation extends *C. elegans* lifespan and promotes mammalian youthfulness

Mechanisms of longevity induced by fatty acid supplementation in wild type *C. elegans*.

Upper panel: PUFA-induced longevity. Supplementation of the ω-6 PUFAs arachidonic acid (AA) and dihomo-γ-linolenic acid (DGLA) promotes longevity in *C. elegans* by inducing autophagy. DGLA and ALA also induce autophagy in mammalian cell culture.

Supplementation of the ω-3 PUFA α-linolenic acid (ALA) extends lifespan through induction of NHR-49/PPARα. The oxidized counterparts of ALA activate the SKN-1/NRF transcription factor. In mice, ALA improves insulin sensitivity. Lower panel: MUFA-induced

longevity. Supplementation of the MUFAs oleic acid, palmitoleic acid, or cis-vaccenic acid is sufficient to extend lifespan through unknown mechanism in wild type *C. elegans*. In mammals, MUFAs prevent inflammation induced by saturated fatty acids. The oleic acid derivative oleoylethanolamide (OEA) extends lifespan by activating transcription factors in *C. elegans*. MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids.

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Figure 4. Lipid metabolism interacts with multiple chromatin modifications

A. Dietary lipids are directly incorporated into histone acyl/acetyl 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, 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. SAM: S-adenosyl methionine.

Table 1.

Lipid changes detected during aging

Lipid class	Organism	Tissue	Change with age	Reference
Cardiolipin	Rat	Brain mitochondria, heart mitochondria	Decrease	[158]
Ceramide	<i>C. elegans</i> , human	Whole worm	Increase	[27,28]
Free fatty acid	Human	Plasma	Increase	[162]
Fatty acids	<i>C. elegans</i>	Whole worm	Down after reproduction	[3]
Phosphatidylcholine	Mouse, rat	Liver, Brain	Decrease	[15,16]
Phosphatidylcholine	<i>C. elegans</i>	Whole worm	Decrease	[3]
Phosphatidylethanolamine	Mouse, rat	Liver, brain, brain mitochondria	Decrease	[15,16]
Phosphatidylethanolamine	<i>C. elegans</i>	Whole worm	Decrease	[3]
Sphingomyelin	Mouse	Liver, Brain	Decrease	[15,16]
Sphingomyelin	<i>C. elegans</i>	Whole worm	Increase in late life	[3]
Triglyceride	Human	Plasma, liver	Increase	[162]
Triglyceride	Rat	Liver, plasma	Increase	[163]
Triglyceride	Mouse	Liver, mitochondria brain	Increase	[5,15,16]