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REVIEW ARTICLE

Lipid metabolism and ageing in *Caenorhabditis elegans*: a complex interplay

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Abstract Life expectancy in Western countries is increasing, with concomitant rise in ageing-related pathologies, including Parkinson's and Alzheimer's disease, as well as other neurodegenerative diseases. Consequently, the medical, psychological and economic burden to society is increasing. Thus, understanding the cellular and molecular mechanisms underlying the association of ageing with elevated vulnerability to disease is crucial towards promoting quality of life in old age. *Caenorhabditis elegans* has emerged as a versatile model to study ageing, due to its simplicity, fast life cycle, and the availability of a wide range of biological tools to target specific genes and cells. Indeed, recent studies in *C. elegans* have revealed that lipid metabolism plays a key role in controlling longevity by impinging on a plethora of molecular pathways and cell types. Here, we summarise findings relevant to the interplay between lipid metabolism and ageing in *C. elegans*, and discuss the implications for the pathogenesis of age-related disorders in humans.

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Introduction

Western societies are facing an increase in life expectancy, with all the challenges that it poses at the medical, psychological and economic level. Extended mean population lifespan is accompanied by increased incidence of age-related disorders, such as Parkinson and Alzheimer diseases (Welsh et al. 2021). At the same time, there is a trend in Western populations towards overweight, obesity and obesity-associated metabolic disorders. Hence, there is an urgent need to understand both the underlying causes of unhealthy ageing, as well as to explore the tight regulation of lipid metabolism (The Lancet Gastroenterology & Hepatology 2021). Moreover, many studies point to a role of lipids as signalling molecules, not only acting as energy reservoirs, and the link between lipid metabolism regulation and lifespan is well-established (Wymann and Schneiter 2008; Möller et al. 2020; Mutlu et al. 2021). Due to its easy-to-handle characteristics and to all the genetic tools and cell mapping available, the soil nematode *Caenorhabditis elegans* has arisen as an excellent model to study both ageing and metabolism (Markaki and Tavernarakis 2020). Thus, in this review we summarise the most relevant research performed in the worm *C.*

elegans during the last 5 years aiming at linking lipid metabolism and ageing, including molecular factors involved in lipid metabolism regulation of ageing (Table 1) and ageing-related diseases (Table 2), as well as the effects of drugs, environmental contaminants and other compounds (Table 3).

Molecular mechanisms involved in lipid metabolism and ageing

Neuronal signalling and metabolism

Neuronal control of lipid metabolism and longevity is under study in mammals and non-mammalian organisms (Ledesma et al. 2011; Jové et al. 2019). Indeed, lipids are known to play many functions in neurons, such as being energy substrates and cellular structural machinery, but also bioactive molecules (reviewed in (Tracey et al. 2018)). Dixit et al. focused on STR-2, a chemosensory G protein-coupled receptor (GPCR) expressed in *C. elegans* AWC and ASI amphid sensory neurons. Interestingly, the mRNA levels of lipase *lipl*-3, Δ-9 desaturases *fat-5*, *fat-6*, and *fat-7* (responsible of conversion of saturated fatty acids [SFAs] to unsaturated fatty acids [UFAs]) and diacylglycerol acyltransferase *dgat-2* (the rate-limiting enzyme for triacylglycerol [TAG] synthesis) were downregulated in *C. elegans* carrying the *str-2(ok3148)* mutation, while acyl-CoA synthetase *acs-2* mRNA levels were upregulated. The *str-2(ok3148)* animals showed decreased intestinal fat storage and were short-lived. Nevertheless, when fat storage raised to wild-type levels by supplementation with monounsaturated fatty acids (MUFAs) (i.e. oleic acid and palmitoleic acid), which are known to be beneficial for longevity, the short-lived phenotype was reversed (Dixit et al. 2020). Moreover, since microtubule regulators are known to play an important role in neuronal function and structure and its abnormal regulation has been associated with age-related disorders in a wide range of animal models (Shamitko-Klingensmith et al. 2016; Apple and Chen 2019; Negrete-Hurtado et al. 2020). Recently, Xu et al. assessed their involvement in lipid metabolism and ageing in *C. elegans*. They found that microtubule worms containing a deletion mutation in the destabilizing gene *hdac-6* were long-lived and displayed exacerbated fat storage, and this phenotype was DAF-16/FOXO-dependent (Xu et al. 2019). On the other hand, Schmeisser et al. focused on muscle cells and its interplay with neurons via muscle-specific bioactive lipid signals (''lipokines") that are generated by muscle-specific phospholipase A_2 (PLA_2) and regulate AMP-dependent protein kinase (AMPK) and the HNF-4-like nuclear receptor NHR-80 in the neuronal tissue to promote metabolic homeostasis and contribute to organism longevity (Schmeisser et al. 2019).

Insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)

The involvement of the life-shortening insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS) pathway in the regulation of longevity and its link with metabolism is well-known (Murphy and Hu 2013; Zečić and Braeckman 2020). In addition, excessive reactive oxygen species (ROS) production has been identified to have a causal effect for obesity and obesity-associated diseases in different animal models, including humans (McMurray et al. 2016). In this line, Wang et al. treated wild-type worms with low concentrations of two toxic chemicals (paraquat or juglone) in order to exacerbate ROS production and observed alterations in fatty acid composition, as well as exaggerated lipid deposition, which was accompanied by overexpression of the stearoyl-CoA desaturase *fat-5*. The authors proposed a mechanism by which increased ROS concentration produced by the mitochondria decreases insulin/IGF-1 transmembrane receptor (IGFR) ortholog DAF-2 activity (i.e. IIS pathway), which elicits the activation of the downstream transcription factor DAF-16/FOXO and, thus, increased *fat-5* expression (Wang et al. 2018).

Notably, Ezcurra et al. described an ageing-inducing mechanism related to the IIS pathway; *C. elegans* consumes its own gut to synthesize yolk, which may be beneficial for reproduction. Nevertheless, this autophagy-dependent intestine-to-yolk biomass conversion has detrimental effects, such as organ atrophy and accumulation of pseudocoelomic lipoprotein pools as a form of intestinal senescent obesity (Ezcurra et al. 2018). These findings support the "hyper-function or run-on" theory of ageing, which considers that ageing is primarily caused by the unnecessary, persistent and deleterious activation of specific signalling pathways, rather than molecular damage (Blagosklonny 2021).

Table 1 Reported studies on molecular factors involved in lipid metabolism and ageing in *Caenorhabditis elegans*

Topic	Main findings	References
Neuronal control of lipid metabolism and longevity	The *str-2(ok3148)* worms displays dysregulation of specific lipid metabolism-related enzymes and fatty acids, decreased intestinal fat storage and shorter lifespan. Supplementation with monounsaturated fatty acids reverses the phenotype	(Dixit et al. 2020)
Neuronal control of lipid metabolism and longevity	The *hdac-6(ok3203)* strain are long-lived and increase fat storage in a DAF-16/FOXO-dependent manner	(Xu et al. 2019)
Neuronal control of lipid metabolism and longevity	Bioactive lipid signals (''lipokines") promote metabolic homeostasis and contribute to organism longevity	(Schmeisser et al. 2019)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	Treatment with paraquat or juglone exacerbates reactive oxygen species production and subsequently alters fatty acid composition	(Wang et al. 2018)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	The autophagy-dependent intestine-to-yolk biomass conversion leads to organ atrophy and accumulation of pseudocoelomic lipoprotein pools	(Ezcurra et al. 2018)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	Expression of *caveolin-1*, as well as the quantity of neuronal caveolae, decreases upon insulin/insulin-like growth factor-1 (IGF-1) signalling reduction. Knockdown of *caveolin-1* promotes longevity	(Roitenberg et al. 2018)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	The anti-ageing effect of phosphatidylcholine supplementation is mediated by the insulin/insulin-like growth factor-1 (IGF-1) signalling pathway and requires DAF-16	(Kim et al. 2019)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	The sphingomyelin synthase SMS-5 and inhibition of LET-607/CREBH activate DAF-16 and induce longevity	(He et al. 2021)
Involvement of insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS)	Supplementation with phosphatidylserine promotes longevity by reducing insulin/insulin-like growth factor-1 (IGF-1) signalling in a DAF-16-dependent manner	(Kim and Park 2020)
Role of intermediates of lipid metabolism	Low levels of C22 glucosylceramide suppress clathrin-dependent autophagic lysosome reformation, which activates TOR pathway and shortens lifespan	(Wang et al. 2021)
Role of intermediates of lipid metabolism	Myo-inositol promotes healthy ageing via *daf-18*, but independently of *daf-16*, and by activating mitophagy	(Shi et al. 2020)
Role of intermediates of lipid metabolism	The *daf-18(yh1)* mutated strain maintains the longevity phenotype associated to attenuated activity of DAF-16/FOXO, and limits the deleterious upregulation of SKN-1/NRF2	(Park et al. 2021)
Mitochondrial function	Supplementation with L-carnitine provokes a SKN-1- and DAF-16-dependent increase in lifespan T08B1.1 acts in a similar manner to L-carnitine	(Liu et al. 2021)

Table 1 (continued)

Topic	Main findings	References
Mitochondrial function	Knockdown of NFYB-1 gives rise to mitochondrial dysfunction, lesser cardiolipin production and shortened lifespan. The phenotype can be reverted by reduction of prosaposin or cardiolipin supplementation	(Tharyan et al. 2020)
Mitochondrial function	Knockdown of either *cytb-5.1* or *cytb-5.2* resulted in decreased fat accumulation with reduced lipid droplet size, less triacylglyceride content, smaller brood size, and shorter lifespan	(He et al. 2018)
Mitochondrial function	Induction of lysosomal lipolysis in worms overexpressing *lipl-4* increases mitochondrial β-oxidation that subsequently lead to fat mobilization and extended lifespan via JUN-1 activity	(Ramachandran et al. 2019)
Mitochondrial function	Maintenance of mitochondrial homeostasis increases fatty acid oxidation and improves lifespan	(Weir et al. 2017)
Mitochondrial function	Both *lipl-5*-depleted and coelomocyte-deficient worms displayed extended lifespan and diminished lipid catabolism upon bacterial deprivation	(Buis et al. 2019)
Mitochondrial function	*lipl-5* controls lipidome composition in normal conditions and in response to starvation by affecting the mitochondrial function	(Macedo et al. 2020b)
Endoplasmic reticulum unfolded protein response	Animals overexpressing XBP-1s show a decrease in triglycerides and an increase in oleic acid, which promotes proteostasis and lifespan extension	(Imanikia et al. 2019)
Endoplasmic reticulum unfolded protein response	XBP-1s drives activation of lipophagy by a conserved RME-1/RAB-10/EHBP-1 complex, which promotes lifespan	(Daniele et al. 2020)
Endoplasmic reticulum unfolded protein response	XBP-1s facilitates lipid depletion in dopaminergic neurons	(Higuchi-Sanabria et al. 2020)
Endoplasmic reticulum unfolded protein response	PAQR-1-depleted worms show increased survival and longevity under endoplasmic reticulum stress	(Kyriakakis et al. 2017)
Adaptation to low temperatures	The *mdt-15(-)* mutants counteract low-temperature-induced longevity and alter expression levels of fatty acid desaturases Feeding with oleic acid alleviates the *mdt-15(-)*-associated reduction in lifespan	(Lee et al. 2019)
Adaptation to low temperatures	Knockdown of *paqr-2* and *nhr-49* reduces lifespan at normal (20 °C) and low (15 °C) temperatures, while *fat-7(wa36)* mutant animals display shortened lifespan only at low temperature	(Chen et al. 2019b)
Adaptation to starvation	Reduction of ceramide levels affects starvation survival. This phenotype is reversed by dietary supplementation with sphingoid bases	(Cui et al. 2017)
Adaptation to starvation	Caloric restriction raises the levels of polyunsaturated fatty acids to mediate longevity	(Chamoli et al. 2020)

Table 1 (continued)

Topic	Main findings	References
Adaptation to starvation	Dustained lipid β-oxidation by overexpressing FLP-7 leads to fat reduction without chronic oxidative stress-related health problems	(Littlejohn et al. 2020)
Targeting of specific genes	Knockdown of *par-1* improves lifespan and health span and decreases intestinal fat content	(Wu et al. 2020)
Targeting of specific genes	Mutation of *sphk-1* reduces lifespan	(Chan et al. 2017)
Targeting of specific genes	Knockdown of FATH-1/C25A1.5 shortens lifespan and suppress lipid droplets formation	(Li et al. 2018)
Targeting of specific genes	Inhibition of acyl-coenzyme A (CoA):cholesterol acyltransferases depletion increases lifespan	(Bai et al. 2020)
Dietary fatty acids	Supplementation with α-linolenic acid extends lifespan via activation of lipid β-oxidation	(Qi et al. 2017)
Dietary fatty acids	Supplementation of Δ6 desaturase activity-defective *fat-3(wa22)* mutants with arachidonic acid increases lifespan	(Guha et al. 2020)
Glucose consumption and metabolism	Lipin 1/LPIN-1 partly counteracts the life-shortening effect of excessive glucose feeding by maintaining the appropriate levels of ω-6 polyunsaturated fatty acids	(Jung et al. 2020)
Glucose consumption and metabolism	High-glucose exposure enhances lipid peroxidation and induces the swelling of mitochondria	(Alcántar-Fernández et al. 2018, 2019)
Glucose consumption and metabolism	Hyperactivation of G3PP restricts lipid deposition and contributes to healthy aging	(Possik et al. 2022)
Epigenetics	Worms lacking SET-2 are long-lived and exhibit increased lipid content, whereas worms lacking RBR-2 are slightly short-lived and show lesser lipid accumulation	(Han et al. 2017)

Table 2 Reported studies on molecular factors involved in lipid metabolism and *Caenorhabditis elegans* models of ageing-related diseases

Topic	Main findings	References
Lewy body dementia	Overexpression of both Aβ and α-synuclein downregulates lipid metabolism- and lysosome-related genes	(Huang et al. 2021)
Alzheimer's disease	Alzheimer's disease models present a switch from glucose to fatty acid metabolism	(Demarest et al. 2020)
Alzheimer's disease	Knockdown of phospholipase D recues Alzheimer's disease phenotype	(Bravo et al. 2018)
Parkinson's disease	NCEH-1 protects dopaminergic neurons from α-synuclein accumulation-mediated neurotoxicity through a mechanism regulating cholesterol homeostasis	(Zhang et al. 2017)
Parkinson's disease	Knockdown of *fat-5* and *fat-7* reverses Parkinson's disease phenotype	(Maulik et al. 2019)
Parkinson's disease	Neuronal lipolysis and polyunsaturated fatty acids ameliorate neurodegeneration	(Yang et al. 2020)

Table 3 Reported studies on drugs, environmental contaminants and other compounds involved in lipid metabolism and ageing in *Caenorhabditis elegans*

Category	Compound studied	References
Pharmacological drugs	Combination of drugs mimicking caloric restriction	(Admasu et al. 2018)
Pharmacological drugs	Mitochondrial Na^+/Ca^{2+} exchanger inhibitor CGP37157	(García-Casas et al. 2021)
Pharmacological drugs	Ferroptosis inhibitors and drugs acting as scavengers to mobilize intracellular iron for extracellular clearance	(Jenkins et al. 2020)
Pharmacological drugs	Inhibitor of the mammalian endocannabinoid (eCB) hydrolase monoacylglycerol lipase (MAGL/MGLL) JZL184	(Chen et al. 2019a)
Nutriceuticals	Heat-inactivated human commensal *Lactobacillus fermentum* BGHV110	(Dinić et al. 2021)
Pharmacological drugs	Aspirin	(Huang et al. 2017)
Pharmacological drugs	Agonists of TFEB	(Wang et al. 2017)
Pharmacological drugs	Deuterated trilinolenin [D-TG(54:9)]	(Beaudoin-Chabot et al. 2019)
Environmental contaminants	Graphene oxide	(Kim et al. 2018)
Environmental contaminants	Phthalates	(How et al. 2019; Pradhan et al. 2018)
Environmental contaminants	Triadimenol	(How et al. 2018)
Environmental contaminants	Tris(1,3-dichloro-2-propyl) phosphate	(Wang et al. 2019)
Environmental contaminants	Metal contaminated soil leachates from an art glass factory	(Rai et al. 2019)
Environmental contaminants	Metformin	(Espada et al. 2020; Pryor et al. 2019)

Furthermore, caveolin-1 (*cav-1*), the gene encoding CAV-1 protein, has been identified as a downstream target of *daf-2*. CAV-1 is known to control lifespan in many organisms. For instance, mice lacking *cav-1* display shortened lifespan (Park et al. 2003) and a plethora of pathological features (Zhao et al. 2002). CAV-1 is a membrane protein mainly expressed in adult *C. elegans* neurons that determines the formation of caveolae, i.e. specific membrane microdomains, also known as lipid rafts, that act as signalling platforms. Roitenberg et al. found that *cav-1* expression, as well as the quantity of neuronal caveolae, decrease upon IIS reduction. Moreover, knockdown of *cav-1* promotes longevity (Roitenberg et al. 2018).

The anti-ageing effect of supplementation with phosphatidylcholine (a glycerolipid/phospholipid which is one of the main components of the cellular membrane) seems to be also mediated by the IIS pathway and requires DAF-16 (Kim et al. 2019). Moreover, the sphingomyelin synthase SMS-5 (that decreases unsaturated phosphatidylcholine levels), as well as suppression of the transcription factor LET-607/CREBH, were found to activate DAF-16 and induce longevity in *C. elegans* (He et al. 2021). Phosphatidylserine is another phospholipid comprising the cellular membrane. Kim et al. reported that worms fed with phosphatidylserine supplementation lived longer, and this effect in longevity was due, at least partially, to reduced IIS, and required DAF-16 (Kim and Park 2020).

Intermediates of lipid metabolism

Lipid metabolism intermediates can modify lifespan by targeting different molecular pathways. The metabolite C22 glucosylceramide, an acyl chain-specific sphingolipid, has been proposed to have a positive effect in longevity, since low levels of C22 glucosylceramide impaired proper membrane localization of clathrin (a protein that regulates membrane budding) and suppressed clathrin-dependent autophagic lysosome reformation, which activated TOR pathway and negatively affected lifespan (Wang et al. 2021). The endogenous metabolite myo-inositol also seems to alleviate ageing. Myo-inositol is the precursor of $PI(4,5)P_2$, which palliates ageing (i.e. increases lifespan, increments mobility and reduces lipid accumulation. $PI(4,5)P_2$ acts through the tumour suppressor gene phosphatase *daf-18* (homologous to mammalian *Pten*), but independently of *daf-16*, and also via activation of mitophagy. On the contrary, $PI(3,4,5)P_3$, that is a derivative from both myo-inositol and $PI(4,5)P_2$, negatively correlates with longevity (Shi

et al. 2020). Interestingly, the missense mutation *daf-18(yh1)* that alters a cysteine to tyrosine in DAF-18 protein maintains the longevity phenotype and, in addition, improves other downstream effects, including those related to motility. At the molecular level, *daf-18(yh1)* maintains the beneficial attenuated activity of DAF-16/FOXO, and also limits the deleterious upregulation of SKN-1/NRF2 (Park et al. 2021).

Lipid metabolism and ageing are also subjected to epigenetic regulation. Trimethylation of lysine 4 on histone H3 (H3K4me3) modifiers alter lifespan and lipid metabolism in different directions; the worms lacking methyltransferase SET-2 (homologue of mammalian SET1) are long-lived and exhibited increased lipid content, whereas worms H3K4me3 demethylase RBR-2 (homologue of mammalian JARID1)- deficient worms are slightly short-lived and show lesser lipid accumulation. Additionally, the levels of the mono-unsaturated fatty acid (MUFA) oleic acid levels, as well as the expression of *fat-5* and *fat-7*, increased after reproduction in *set-2*-depleted animals. Consequently, dietary supplementation of individual mono-unsaturated fatty acids (MUFAs) (oleic, palmitoleic or cis-vaccenic acid was sufficient for longevity, whereas dietary supplementation of the polyunsaturated fatty acids (PUFAs) linoleic and α-linolenic acid did not affect lifespan (Han et al. 2017).

Mitochondrial function

The relevance of mitochondrial lipid β-oxidation for healthy ageing has been widely studied, especially in caloric restriction conditions. Indeed, reduction of caloric intake seems to be a promising therapeutic approach in nematodes (Macedoet al. 2020a) and also in *Drosophila* (Sohal and Weindruch 1996), rats (Faitg et al. 2019) and mice (Lanza et al. 2012). At the mechanistical level, mitochondrial lipid β-oxidation has been recently further assessed by Liu et al., who fed *C. elegans* with L-carnitine, a mediator of fatty acids transport into the mitochondria for β-oxidation, and observed a SKN-1- and DAF-16-dependent increase in lifespan, concomitant to improved resistance to oxidative stress during ageing. In addition, the authors discovered T08B1.1 (probably evolutionary related to human carnitine transporter OCTN1), which acts in a similar manner to L-carnitine (Liu et al. 2021). Moreover, supplementation with α-linolenic acid, ω-3 polyunsaturated fatty acid, resulted in extended lifespan via the activation of the nuclear hormone receptor-49 (NHR-49) that led to the expression of genes involved in β-oxidation of lipids (Qi et al. 2017). Supplementation of Δ6 desaturase activity-defective *fat-3(wa22)* mutants with arachidonic acid and ω-3 d arachidonic acid (since this strain cannot synthesize them) also increased lifespan in a study performed by Guha et al. (2020) However, previous reports have shown that trans fat diet negatively affects lifespan of *fat-3 mutants* (Reisner et al. 2011), highlighting the contrasting roles of each specific lipid compound for health span and lifespan regulation.

In the same line of linking lipid metabolism, ageing and mitochondrial function, Tharyan et al. reported that knockdown of a subunit of the NF-Y transcriptional complex named nuclear transcription factor Y, beta subunit (NFYB-1) by RNAi gives rise to mitochondrial dysfunction, lesser cardiolipin production and shortened lifespan. The detrimental effects of NFYB-1 depletion were reverted by reducing lysosomal prosaposin (a regulator of glycosphingolipid metabolism that is inhibited by NFYB-1) or by cardiolipin supplementation (Tharyan et al. 2020). Likewise, He et al. showed that RNAi knockdown of either cytochrome b5 *cytb-5.1* or *cytb-5.2* resulted in decreased fat accumulation with reduced lipid droplet size, less triacylglyceride content, smaller brood size, and shorter lifespan in both parental and F1 generation animals, due to dysregulation of stearoyl-CoA desaturase (i.e. FAT-1, FAT-4, FAT-5, FAT-6/7) that participate in the biosynthesis of unsaturated fatty acids (UFAs) (He et al. 2018). Furthermore, when lysosomal lipolysis was induced in worms constitutively overexpressing the lysosomal acid lipase *lipl-4*, Ramachandran et al. detected an increase in mitochondrial β-oxidation that subsequently lead to fat mobilization and extended lifespan. Remarkably, this effect was mediated by the transcription factor JUN-1 in the cell nucleus (Ramachandran et al. 2019). Indeed, Weir et al. also explored the role of mitochondria on ageing and focused on the crosstalk between mitochondria and peroxisomes, concluding that maintaining mitochondrial homeostasis (which includes mitochondrial fusion and fission) increases fatty acid oxidation and it has a positive effect on the nematode lifespan, since mitochondrial homeostasis

is necessary for AMPK and dietary restriction-mediated longevity (Weir et al. 2017).

In addition to *lipl-4*, the role of *lipl-5* in metabolism-regulated lifespan has been dissected, with special focus on coelomocytes. Coelomocytes are located in the fluid-filled body cavity (i.e. coelom) of the worms and act as scavenger cells by performing phagocytosis and other killing mechanisms (Homa 2018). Both worms carrying a genetic deletion of *lipl-5* (a lipase predominantly localized in coelomocytes) and coelomocyte-deficient worms displayed extended lifespan and diminished lipid catabolism upon bacterial deprivation, which was probably mediated by similar or overlapping molecular mechanisms, since simultaneous silencing of *lipl-5* and coelomocyte did not enhance the phenotype (Buis et al. 2019). Furthermore, *lipl-5* was found to control lipidome composition in normal conditions and in response to starvation by affecting the mitochondrial function (Macedo et al. 2020b).

Endoplasmic reticulum unfolded protein response

Endoplasmic reticulum unfolded protein response (UPR^{ER}) encompasses alterations in protein translation and membrane lipid synthesis that are affected by ageing both in mammals and nematodes (reviewed in (Estébanez et al. 2018)). For example, UPR^{ER}- associated changes in lipid metabolism are age-dependent in the murine liver (Ward et al. 2022) and in nematodes (Imanikia et al. 2019). Imanikia et al. analysed animals constitutively overexpressing neuronal XBP-1s, an endoplasmic reticulum unfolded protein response (UPR^{ER}) transcription factor XBP-1, and observed enhanced lipase and Δ9 desaturase FAT-6 activity in the intestinal lysosomes, which led to a decline in triglycerides and an increase in oleic acid, which further promoted proteostasis and lifespan extension. Moreover, Dietary intake of oleic acid induced longevity in the lifespan in wild-type by safeguarding protein homeostasis, but not in *xbp-1s*-overexpressing worms (Imanikia et al. 2019). Additional, neuronal XBP-1s was also found to drive activation of lipophagy by a conserved RME-1/RAB-10/EHBP-1 complex, which had a positive effect on lifespan (Daniele et al. 2020). The effect of XBP-1s on lifespan was related to its role in dopaminergic neurons, where it facilitates lipid depletion (therefore promoting lipid homeostasis), and in serotonergic neurons, where it underlies protein homeostasis (Higuchi-Sanabria et al. 2020). The adiponectin receptor PAQR-1 has also been linked to the canonical ER unfolded protein response (UPR^{ER}) pathway, since PAQR-1-depleted worms show increased survival and longevity under endoplasmic reticulum stress (Kyriakakis et al. 2017).

Adaptation to stress stimuli

Lipid mediators and lipid metabolism is also involved in adaptation to stresses such as low temperatures or starvation. Lee et al. studied the role of the transcriptional coregulator mediator subunit 15 (MDT-15/MED15) at low temperatures and discovered that *mdt-15(-)* mutants prevented low-temperature-induced longevity and altered expression levels of fatty acid desaturases. Further data confirmed that MDT-15 upregulates the fatty acid desaturase *fat-7*. Furthermore, Lee et al. reported that *mdt-15(-)* mutants display a reduction in the unsaturated fatty acids (UFAs) /saturated fatty acids (SFAs) (UFA/SFA) ratio that suppresses longevity, probably by disturbing proteostasis. Feeding with exogenous oleic acid alleviated the *mdt-15(-)*-associated reduction in lifespan. Altogether these results shed light into the mechanisms underpinning low-temperature-induced longevity (Lee et al. 2019).

Low temperatures have also been shown to affect lifespan of specific lipid metabolism-related knockdown worms. For example, animals subjected to RNAi knockdown of adiponectin receptor *paqr-2* and nuclear hormone receptor-49 *nhr-49* exhibited reduced lifespan at normal (20 °C) and low (15 °C) temperatures, while stearic CoA desaturase-encoding *fat-7(wa36)* mutant animals displayed shortened lifespan only at low temperature (Chen et al. 2019b). Further research into the role of adiponectin receptor PAQR-2 (homolog of mammalian AdipoR2) in low temperature adaptation revealed that PAQR-2 senses drops in temperature and activates downstream signalling that converge in the transcriptional activator NHR-49. NHR-49 upregulates the transcription of the stearic CoA desaturase-encoding gene *fat-7* and FAT-7 catalyses fatty acid desaturation, generating the ω-6 PUFAs γ-linolenic acid and arachidonic acid. These two ω-6 PUFAs activate autophagy and enhancement of autophagy delays the ageing-related decrease in collagen levels in the epidermis to induce longevity (Chen et al. 2019b).

Other conditions, such as starvation (i.e. caloric restriction), are also known to improve health span and lifespan (Hofer et al. 2022). Ceramides, which are lipids composed by a sphingoid base linked to a fatty acid, are necessary for the adequate expression of genes known to be regulated by the IIS pathway, since reduction of ceramide levels caused by mutations in genes involved in ceramide synthesis affected starvation survival of first larval stage (L1) animals. This phenotype was reversed by dietary supplementation with sphingoid bases (Cui et al. 2017). Indeed, caloric restriction has been demonstrated to raise the levels of polyunsaturated fatty acids (PUFAs), particularly linoleic acid (LA) and eicosapentaenoic acid (EPA), which activate the p38 mitogen-activated protein kinase (p38-MAPK) pathway that upregulate the cytoprotective (CyTP) genes. This model has been related to caloric restriction-mediated longevity (Chamoli et al. 2020). Importantly, loss of weight is recommended to obese individuals and it involves of chronic lipid β-oxidation. Littlejohn et al. established a *C. elegans* model of sustained lipid β-oxidation by overexpressing FLP-7/NPR-22 tachykinin neuron-to-intestine signalling pathway. The *flp-7*-overexpressing worms exhibited a fat reduction which was dependent on the presence of the intestinal triglyceride lipase ATGL-1. According to their data, ATGL-1 activates a feedback loop involving the mito-nuclear transcription factor ATFS-1 and HLH-11/AP4 (a repressor of ATGL-1 discovered by the authors). This loop allows β-oxidation to be long-lasting without negatively affecting longevity, which entails an important mechanism to understand why weight loss does not lead to health problems related to oxidative stress, although it requires sustained lipid β-oxidation (Littlejohn et al. 2020).

Targeting of specific genes

Some studies have been focussing on the role of specific genes/proteins on linking lipid metabolism and ageing. In this sense, Wu et al. attempted to decipher the role of serine/threonine kinase PAR-1, which is crucial during development, in late larval- early adult (L4) worms. They found that *par-1* knockdown had a beneficial effect in lifespan and health span, and give rise to age-dependent AMPK activation and lesser intestinal fat content (Wu et al. 2020).

Knockdown of a wide range of genes encoding enzymes that participate in lipid metabolism has been shown to alter lifespan, although molecular mechanisms are still unclear. In this sense, sphingosine kinase (sphk-1) mutation provoked a reduced lifespan phenotype in worms (Chan et al. 2017). Furthermore, worms lacking FATH-1/C25A1.5 (homolog of mammalian fatty acid 2-hydroxylase [FA2H], the enzyme catalysing the first step of fatty acid α-oxidation to generate sphingolipids containing 2-hydroxy fatty acyl moieties) displayed shortened lifespan and suppression of lipid droplets formation in the intestine, with a specific decrease in heptadecenoic acid. Interestingly, and contrary to what has been observed in other models (Dixit et al. 2020), dietary supplementation with heptadecenoic acid (C17:1), but not oleic acid (C18:1), mitigated the *fath-1* knockdown-mediated defects (Li et al. 2018). Finally, Bai et al. analysed the effect of acyl-coenzyme A (CoA):cholesterol acyltransferases (ACATs) depletion in worms in normal feeding conditions and during fasting. In the first case, they observed diminished lipid accumulation, while in the second case they found hyperactivation of lipolysis and also an increase in lifespan, highlighting the potential beneficial effect of ACATs inhibition, partly through targeting of the (IIS) pathway (Bai et al. 2020).

Glucose consumption and metabolism

The phosphatidic acid phosphatase Lipin 1/LPIN-1 is an important enzyme for triglyceride synthesis. Jung et al. discovered that Lipin 1/LPIN-1 partly counteracts the life-shortening effect of excessive glucose feeding by maintaining the appropriate levels of ω-6 polyunsaturated fatty acids (PUFAs) (i.e. linoleic acid and arachidonic acid), which are protective against the detrimental effects of high-glucose diet (Jung et al. 2020). The effect of excessive glucose-diets on worms have been further analysed in two studies from the same group, concluding that high-glucose exposure enhances lipid peroxidation and induces the swelling of mitochondria (Alcántar-Fernández et al. 2018; Alcántar-Fernández et al. 2019). The authors also confirmed the excessive glucose-associated short lifespan phenotype, which could be modified by altering the glucose composition of the diet or by mutating or inhibiting transcription factors involved in carbohydrate and lipid metabolism, oxidative stress and

longevity (i.e. HIF-1/HIF1α, CRH-1/ CREB, CEP-1/ p53, SKN-1/NRF2, SBP-1/SREBP and DAF-16/ FOXO) (Alcántar-Fernández et al. 2018).

Regarding glucose metabolism, Possik et al. focused on glycerol-3-phosphate phosphatase (G3PP), the enzyme that hydrolyzes glucose-derived glycerol-3-phosphate to glycerol, and found that hyperactivation of the G3PP restricts lipid deposition and contributes to healthy aging in a similar manner to caloric restriction, but without affecting fertility, suggesting its potential as a target for ageing-related metabolic diseases (Possik et al. 2022).

Caenorhabditis elegans models of age-associated diseases and its connection with lipid metabolism

Lewy body dementia

Disturbed lipid metabolism has been related to ageing-associated neurodegenerative. In the case of Lewy body dementia (DLB), patients co-express amyloid β (Aβ) and α-synuclein (α-syn) in the brain. Huang et al. performed transcriptomics in nematodes co-expressing human Aβ and α-syn with alanine 53 to threonine mutation (*α-syn(A53T)*) in pan-neurons and in the lateral temporal lobe of post-mortem brains of patients with DLB, and in both cases they found downregulation in lipid metabolism- and lysosome-related genes (Huang et al. 2021). Thus, they suggested that, considering that lysosomes promote lipid catabolism and transport in order to preserve cellular lipid homeostasis (Thelen and Zoncu 2017), aberrant lysosomal function may play a role in DLB pathogenesis (Huang et al. 2021).

Alzheimer's disease

Regarding Alzheimer's disease, data from *C. elegans* models, as well as mice and human patients, indicate a switch from glucose to fatty acid metabolism (which probably takes place in the glia to counterbalance the neuronal glucose hypometabolism) that may be a compensatory neuroprotective metabolic mechanism in this specific pathological context (Demarest et al. 2020). Remarkably, abolishment of the activity of phospholipase D, the enzyme that hydrolyses phosphatidylcholine to form phosphatidic acid and choline, partially recued the pathological phenotype of Alzheimer's disease worm models (Bravo et al. 2018).

Parkinson's disease

Parkinson's disease is also an ageing-related disease and its pathogenesis is due to the overexpression and abnormal aggregation of α-syn (Chen et al. 2022). Interesting research has been recently performed in nematode models of Parkinson disease. The neutral cholesterol ester hydrolase 1 (NCEH-1) acts downstream of the IIS pathway (more specifically, downstream of DAF-2) and protects dopaminergic neurons from α-syn accumulation-mediated neurotoxicity through a mechanism regulating cholesterol homeostasis. Despite of the positive effect of NCEH-1 in health span, it does not seem to impact lifespan (Zhang et al. 2017). Parkinson's disease pathology has been further explored by Maulik et al. They silenced the Δ9 desaturase-encoding genes *fat-5* and *fat-7* and, as expected, observed a decline in total fat content. Silencing of *fat-5* and *fat-7* partially reverted the pathological phenotype of a plethora of Parkinson's disease worm models without having significant effect on the lifespan (Maulik et al. 2019). Thus, similarly to what was described by Zhang et al. (2017), health span, but not lifespan, was ameliorated (Maulik et al. 2019).

Lipid droplets are rare in healthy neurons, but they have been reported in disease models of Parkinson's disease, Huntington's disease and other neural pathological conditions. In order to understand the mechanism underlying the appearance of lipid droplets and its consequences for neural function, Yang et al. generated nematodes carrying mutations in the lipolysis genes *atgl-1* and *lid-1* and observed that these mutants display lipid droplets in their neurons. Both mutations in *atgl-1* and *lid-1* reduced biosynthesis of polyunsaturated fatty acids (PUFAs) and ameliorated neurodegeneration triggered by the expression a dominant negative form of the ion-channel protein MEC-4 and stimulated PUFA partitioning toward triacylglycerol. In addition, the authors observed that PUFAs increased neurodegeneration through incorporation into phospholipids, suggesting that neuronal lipolysis and PUFAs are fundamental for cell-autonomous regulation of neural functions and neurodegeneration (Yang et al. 2020).

Effects of drugs and other compounds

Importantly, many compounds have been tested to analyse whether they have a lipid metabolism-dependent anti-ageing effect. A combination of drugs targeting pathways such as those involving AMPK, mechanistic target of rapamycin (mTOR) and c-Jun N-terminal kinases (JNK), mimicking caloric restriction and modulating mitochondrial metabolism were found to counteract ageing in a synergic manner via the increase of monounsaturated fatty acids (MUFAs) and medium-chain-fatty-acyl-containing triacylglycerols (TAGs) (Admasu et al. 2018). With respect to mitochondrial targeting, treatment of worms with the mitochondrial Na^+/Ca^{2+} exchanger inhibitor CGP37157, which has been reported to extend lifespan, also induced changes in lipid metabolism enzymes expression, although these alterations at the transcriptomic level have not been further explored (García-Casas et al. 2021).

Additionally, treatment of *C. elegans* with both ferroptosis inhibitors and with drugs acting as scavengers to mobilize intracellular iron for extracellular clearance were found to protect against lipid peroxidation and to promote longevity (Jenkins et al. 2020). Moreover, the inhibitor of the mammalian endocannabinoid (eCB) hydrolase monoacylglycerol lipase (MAGL/MGLL) JZL184 extends lifespan of *C. elegans* by targeting the degrading eCB-related monoacylglycerides enzyme FAAH-4. Thus, although FAAH-4 does not show homology with mammalian MAGL, it performs the same function and can be targeted by JZL184 to positively modulate ageing (Chen et al. 2019a). Nutriceutical approaches have also been explored. Dietary consumption of heat-inactivated human commensal *Lactobacillus fermentum* BGHV110, which is part of the gut microbiota, was beneficial for nematode lifespan and health span and altered lipid metabolism via HLH-30-mediated reduction of the content of lipid droplets (Dinić et al. 2021). *C. elegans* has been used to provide insights into molecular mechanisms underlying the effects of the commonly used drug aspirin. Aspirin was found to promote longevity, decrease lipid content and enhance expression of lipid hydrolysis and fatty acid β-oxidation-related genes via DAF-12 and DAF-16 (Huang et al. 2017).

Additionally, new drugs affecting regulators of lipid metabolism and promoting lifespan extension are currently under study. For example, agonists of the lipid metabolism master regulator small-molecule transcription factor EB (TFEB) may potentially be used as a treatment of metabolic and ageing-related disorders (Wang et al. 2017), while deuterated trilinolenin [D-TG(54:9)], which are chemically reinforced essential fatty acids, have been proposed as dietary supplements (Beaudoin-Chabot et al. 2019).

Effects of environmental contaminants

Kim et al. studied the effect of the environmental contaminant graphene oxide in *C. elegans*, concluding that it alters fatty acid metabolism (Kim et al. 2018). Graphene oxide is a chemically-modified graphene with several potential applications, but whose safety for live organisms and the environment is yet to be demonstrated. Upon exposure to graphene oxide, Kim et al. found that intestinal lipid storage, as well as a panel of fatty acid metabolites, were decreased in wild-type worms, while there was a reduction and extension of the lifespan of long-lived *fat-5(tm420)* mutants and short-lived *nhr-49(nr2041)* mutants, respectively (Kim et al. 2018).

Phthalates are used in cosmetics and other personal care products and they are also present in food and constructions. Nevertheless, it seems probably that they can impact negatively human and animal health. In this line, Pradhan et al. exposed worms to di(2-ethylhexyl) phthalate and diethyl phthalate from first larval stage (L1) to throughout their life and detected many alterations in physiological functions, such as dysregulation of expression of genes involved in stress response and lipid metabolism, increased lipid deposition, defective reproduction and shortened lifespan. Remarkably, both compounds affected *C. elegans* in a similar manner, suggesting that replacing the widely-used di (2-ethydlhexyl) phthalate with diethyl phthalate will not be safer for animal health (Pradhan et al. 2018). Moreover, How et al. identified the IIS pathway and SKN-1 as mediators of the accelerated ageing observed in worms upon exposure to di(2-ethylhexyl) phthalate (How et al. 2019).

Chronic exposure to nematodes to the widely-spread agricultural fungicide triadimenol led to similar results in terms of stress response, reproduction

and lifespan to those observed after treatment with phthalates. In addition, triadimenol exposure from first larval stage (L1) to death increased increment aging biomarkers (i.e. lipofuscin, lipid peroxidation, and ROS), as well as DAF-16 nuclear localization. Inactivating mutation of *daf-2* reversed the deleterious accumulation of lipofuscin, whereas mutation of *daf-16* increased lipofuscin in triadimenol-treated aged worms. Thus, the effect of triadimenol on ageing was dependent on IIS pathway (How et al. 2018). Moreover, environmental pollution by the tris(1,3-dichloro-2-propyl) phosphate from plastics, textiles and varnishes, among other products, has also raised concerns about its effect on human and animal health. Wang et al. reported signs of degeneration, such as altered locomotion and shortened lifespan, as well as biomarkers of aging (i.e. lipofuscin and lipid peroxidation products), in first larval stage (L1) worms exposed to tris(1,3-dichloro-2-propyl) phosphate for 72 h. Furthermore, the authors proposed glutathione S-transferase (GST) as the enzyme involved in detoxification of the environmental contaminant in *C. elegans* (Wang et al. 2019). The effects of contaminations in specific regions has also been studied. Rai et al. treated worms with metal contaminated soil leachates from an art glass factory in Sweden to assess the toxicity of this environment. Both after short (6 h for late larval- early adult [L4] worms) or long exposure (48 h to first larval stage [L1]) animals displayed altered gene expression in genes related to stress response and lipid metabolism. Moreover, lipid metabolism dysregulation correlated with decreased longevity (Rai et al. 2019).

Interestingly, metformin has been proposed as a life-extending treatment in healthy individuals. Nevertheless, Espada et al. found that metformin has opposite effects depending on the age of the worms: its increases lifespan in young organisms, but it shortens lifespan in late life. This deleterious effect in late life may be caused by the metformin-induced alteration of mediators of lipid metabolism in aged worms (Espada et al. 2020). Furthermore, microbiota signalling has also been proposed to play a role in modulation the effect of metformin therapy by increasing both fatty acid oxidation and lifespan, probably through the transcriptional regulator Crp (Pryor et al. 2019).

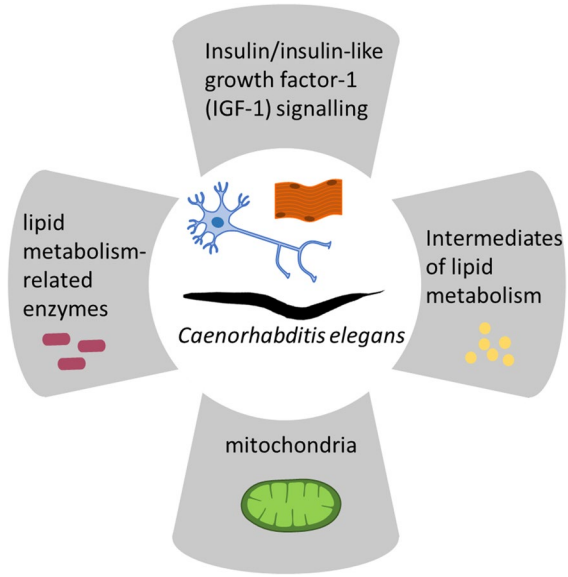

Fig. 1 Schematic representation of the main molecules and organelles linking lipid metabolism and ageing in *Caenorhabditis elegans* according to the literature mentioned in this review

Conclusions

Lipid metabolism controls ageing and age-related disorders by using a variety of mechanisms, ranging from food sensing to epigenetic modification, that affect activity and content of lipid metabolism-related enzymes and specific metabolites (Fig. 1). It is now obvious that these lipidic metabolites are not only energy stores, but many of them act as cellular signalling molecules.

In this review, we survey recent studies in *C. elegans* that provide useful insights, implicating impaired lipid metabolism and homeostasis in the pathogenesis of age-associated pathologies (Fig. 2). The use of this simple and easy-to-handle animal model provides interesting mechanistical insights. Importantly, these studies contributed to further dissect the complex interplay between many organs in lipid metabolism-mediated ageing regulation, such as muscle and neurons (Schmeisser et al. 2019) and intestine (Ezcurra et al. 2018), where lipid droplets are stored. Furthermore, when looking at the subcellular level, different organelles have been shown to be involved in the process, including

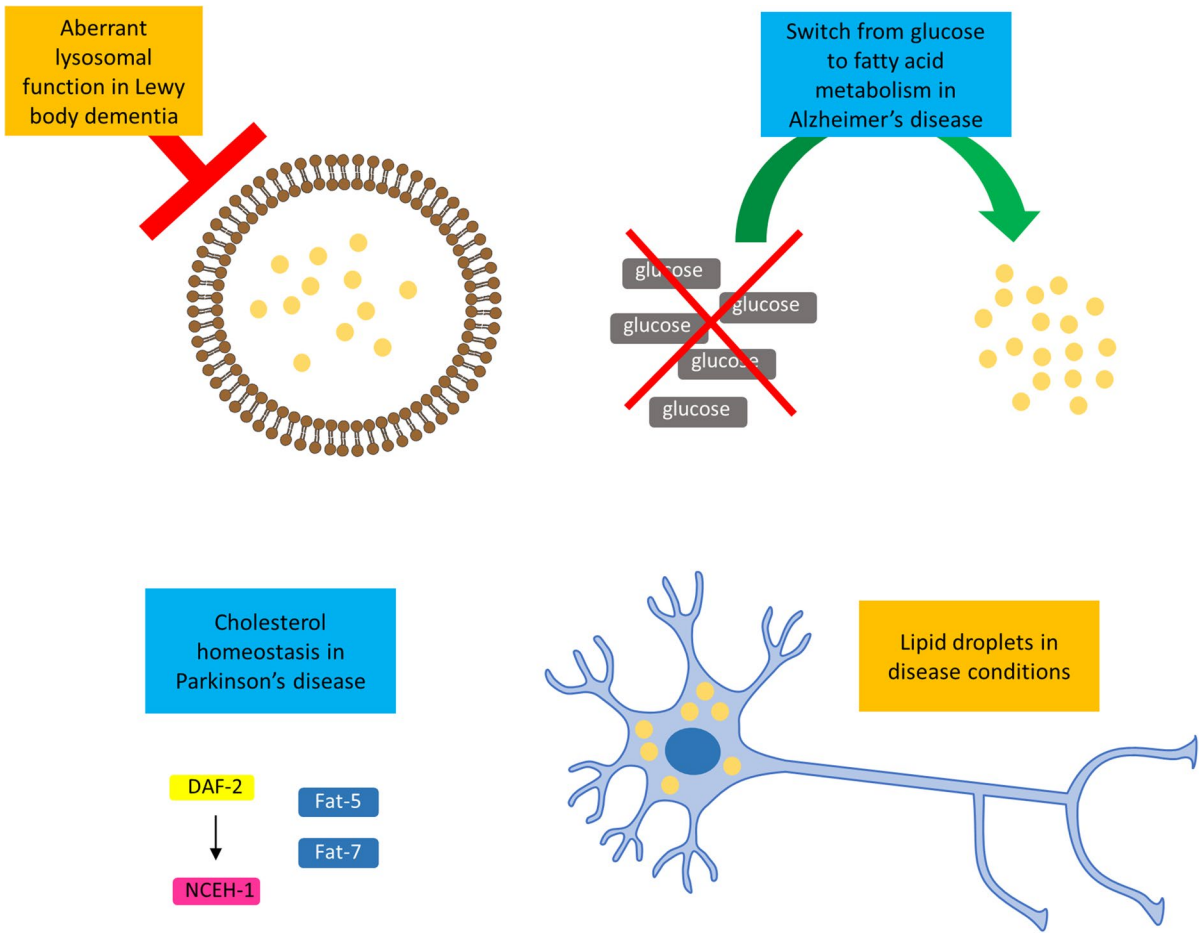

Fig. 2 Schematic representation of lipid metabolism-related pathological mechanisms in age-associated diseases according to the literature mentioned in this review

mitochondria, through a wide range of mechanisms but mainly lipid oxidation (Liu et al. 2021), and also peroxisomes (Weir et al. 2017) and lysosomes (Huang et al. 2021). Moreover, lipid metabolism and ageing are closely related to proteostasis (Imanikia et al. 2019), ROS production (Wang et al. 2018) and glucose metabolism (Alcántar-Fernández et al. 2018; Alcántar-Fernández et al. 2019), the latest being also relevant for the pathogenesis of Alzheimer's disease (Bravo et al. 2018).

Additionally, compelling evidence points to the potential use of specific lipids and nutraceutical approaches, as well as specific drugs, as therapeutic interventions. Regarding lipids, MUFAs (such as oleic acid and palmitoleic acid) (Dixit et al. 2020), α-linolenic acid (Qi et al. 2017), phosphatidylcholine (Kim et al. 2019), phosphatidylserine (Kim and Park 2020) and cardiolipin (Tharyan et al. 2020) have been suggested to have anti-ageing activity. Thus, increasing intake of these specific lipids either by shifting our diets towards higher amounts of the food products containing them or by consumption of the lipids as dietary supplements could be an affordable and simple approach to attenuate ageing. Recent findings also provide a better understanding of the molecular mechanisms governing conditions that are known to promote ageing: i.e. low temperatures and caloric restriction (Table 1). Additionally, newly discovered molecules, such as T08B1.1, which seems to act similarly to L-carnitine (Liu et al. 2021), are coming into the frame.

Of note, new studies also shed light on the detrimental effects of environmental contaminants (Table 3). This evidence provides a scientific base to raise awareness of the stakeholders (which are all citizens worldwide) and pressure the corresponding organizations to make policies against the use of these products. Therefore, even in the cases were no molecular mechanisms are explored, worm models are useful to screen lipid metabolism-related modulators of lifespan. Nevertheless, a better mechanistical understanding of the processes, as well as data from mammalian systems, are needed in order to proceed to clinical translation of the discoveries. In any case, further research is need to clarify whether any of these findings can be used as potential therapies to promote health span and prevent ageing.

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Declarations

Competing interests The authors declare no competing interests.

References

Admasu TD et al (2018) Drug synergy slows aging and improves healthspan through IGF and SREBP lipid signaling. Dev Cell 47(1):67-79.e5. https://doi.org/10.1016/j.devcel.2018.09.001

Alcántar-Fernández J et al (2018) *Caenorhabditis elegans* respond to high-glucose diets through a network of stress-responsive transcription factors. PLoS ONE. https://doi.org/10.1371/journal.pone.0199888

Alcántar-Fernández J et al (2019) High-glucose diets induce mitochondrial dysfunction in *Caenorhabditis elegans*. PLoS ONE. https://doi.org/10.1371/journal.pone.0226652

Apple E, Chen L (2019) Neuronal microtubules impact lifespan. Aging. https://doi.org/10.1016/bs.ircmb.2015.09.004

Bai J et al (2020) *C. elegans* ACAT regulates lipolysis and its related lifespan in fasting through modulation of the genes in lipolysis and insulin/IGF-1 signaling. BioFactors 46(5):754–765. https://doi.org/10.1002/biof.1666

Beaudoin-Chabot C et al (2019) Deuterated polyunsaturated fatty acids reduce oxidative stress and extend the lifespan of *C. elegans*. Front Physiol. https://doi.org/10.3389/fphys.2019.00641

Blagosklonny MV (2021) The hyperfunction theory of aging: three common misconceptions. Available from: https://pubmed.ncbi.nlm.nih.gov/34549076/

Bravo FV et al (2018) Phospholipase D functional ablation has a protective effect in an Alzheimer's disease *Caenorhabditis elegans* model. Sci Rep. https://doi.org/10.1038/s41598-018-21918-5

Buis A et al (2019) Coelomocytes regulate starvation-induced fat catabolism and lifespan extension through the lipase LIPL-5 in *Caenorhabditis elegans*. Cell Rep 28(4):1041-1049.e4. https://doi.org/10.1016/j.celrep.2019.06.064

Chamoli M et al (2020) Polyunsaturated fatty acids and p38-MAPK link metabolic reprogramming to cytoprotective gene expression during dietary restriction. Nat Commun. https://doi.org/10.1038/s41467-020-18690-4

Chan JP et al (2017) Loss of sphingosine kinase alters life history traits and locomotor function in *Caenorhabditis elegans*. Front Genet. https://doi.org/10.3389/fgene.2017.00132

Chen AL et al (2019a) Pharmacological convergence reveals a lipid pathway that regulates *C. elegans* lifespan. Nat Chem Biol 15(5):453–462. https://doi.org/10.1038/s41589-019-0243-4

Chen YL et al (2019b) Adiponectin receptor PAQR-2 signaling senses low temperature to promote *C. elegans* longevity by regulating autophagy. Nat Commun. https://doi.org/10.1038/s41467-019-10475-8

Chen R, Gu X, Wang X (2022) α-Synuclein in Parkinson's disease and advances in detection. Clin Chim Acta 529:76–86. https://doi.org/10.1016/j.cca.2022.02.006

Cui M et al (2017) Starvation-induced stress response is critically impacted by ceramide levels in *Caenorhabditis elegans*. Genetics 205(2):775–785. https://doi.org/10.1534/genetics.116.194282

Daniele JR et al (2020) UPR ER promotes lipophagy independent of chaperones to extend life span. Available from: https://www.science.orghttps://pubmed.ncbi.nlm.nih.gov/31911951/

Demarest TG et al (2020) Biological sex and DNA repair deficiency drive Alzheimer's disease via systemic metabolic remodeling and brain mitochondrial dysfunction. Acta Neuropathol 140(1):25–47. https://doi.org/10.1007/s00401-020-02152-8

Dinić M et al (2021) Host–commensal interaction promotes health and lifespan in *Caenorhabditis elegans* through the activation of HLH-30/TFEB-mediated autophagy. Aging 13(6):8040–8054

Dixit A et al (2020) Neuronal control of lipid metabolism by STR-2 G protein-coupled receptor promotes longevity in *Caenorhabditis elegans*. Aging Cell. https://doi.org/10.1111/acel.13160

Espada L et al (2020) Loss of metabolic plasticity underlies metformin toxicity in aged *Caenorhabditis elegans*. Nat Metab 2(11):1316–1331. https://doi.org/10.1038/s42255-020-00307-1

Estébanez B et al (2018) Endoplasmic reticulum unfolded protein response, aging and exercise: an update. Front Physiol 9:1744. https://doi.org/10.3389/FPHYS.2018.01744

Ezcurra M et al (2018) *C. elegans* eats its own intestine to make yolk leading to multiple senescent pathologies. Curr Biol 28(16):2544-2556.e5. https://doi.org/10.1016/j.cub.2018.06.035

Faitg J et al (2019) Effects of aging and caloric restriction on fiber type composition, mitochondrial morphology and dynamics in rat oxidative and glycolytic muscles. Front Physiol 10:420. https://doi.org/10.3389/fphys.2019.00420

García-Casas P et al (2021) The mitochondrial Na+/Ca2+ exchanger inhibitor CGP37157 preserves muscle structure and function to increase lifespan and healthspan in *Caenorhabditis elegans*. Front Pharmacol. https://doi.org/10.3389/fphar.2021.695687

Guha S et al (2020) Juniperonic acid biosynthesis is essential in *Caenorhabditis elegans* lacking Δ6 desaturase (fat-3) and generates new ω-3 endocannabinoids. Cells. https://doi.org/10.3390/cells9092127

Han S et al (2017) Mono-unsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. Nature 544(7649):185–190. https://doi.org/10.1038/nature21686

He B et al (2018) Identification of cytochrome b5 CYTB-5.1 and CYTB-5.2 in *C. elegans*; evidence for differential regulation of SCD. Biochim Biophys Acta Mol Cell Biol Lipids 1863(3):235–246. https://doi.org/10.1016/j.bbalip.2017.12.007

He B et al (2021) Phosphatidylcholine mediates the crosstalk between LET-607 and DAF-16 stress response pathways. PLoS Genet. https://doi.org/10.1371/journal.pgen.1009573

Higuchi-Sanabria R et al (2020) Divergent nodes of non-autonomous UPRER signaling through serotonergic and dopaminergic neurons. Cell Rep. https://doi.org/10.1016/j.celrep.2020.108489

Hofer SJ et al (2022) The ups and downs of caloric restriction and fasting: from molecular effects to clinical application. EMBO Mol Med. https://doi.org/10.15252/emmm.202114418

Homa J (2018) Earthworm coelomocyte extracellular traps: structural and functional similarities with neutrophil NETs. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2787-0

How CM, Li SW, Liao VHC (2018) Chronic exposure to triadimenol at environmentally relevant concentration adversely affects aging biomarkers in *Caenorhabditis elegans* associated with insulin/IGF-1 signaling pathway. Sci Total Environ 640–641:485–492. https://doi.org/10.1016/j.scitotenv.2018.05.314

How CM et al (2019) Early life exposure to di(2-ethylhexyl) phthalate causes age-related declines associated with insulin/IGF-1-like signaling pathway and SKN-1 in *Caenorhabditis elegans*. Environ Pollut 251:871–878. https://doi.org/10.1016/j.envpol.2019.04.141

Huang XB et al (2017) Aspirin increases metabolism through germline signalling to extend the lifespan of *Caenorhabditis elegans*. PLoS ONE. https://doi.org/10.1371/journal.pone.0184027

Huang X et al (2021) Human amyloid beta and α-synuclein co-expression in neurons impair behavior and recapitulate features for Lewy body dementia in *Caenorhabditis elegans*. Biochim Biophys Acta Mol Basis Dis. https://doi.org/10.1016/j.bbadis.2021.166203

Imanikia S et al (2019) XBP-1 remodels lipid metabolism to extend longevity. Cell Rep 28(3):581-589.e4. https://doi.org/10.1016/j.celrep.2019.06.057

Jenkins NL et al (2020) Changes in ferrous iron and glutathione promote ferroptosis and frailty in aging *Caenorhabditis elegans*. Elife 9:1–28. https://doi.org/10.7554/eLife.56580

Jové M et al (2019) Lipids and lipoxidation in human brain aging. Mitochondrial ATP-synthase as a key lipoxidation target. Redox Biol. https://doi.org/10.1016/J.REDOX.2018.101082

Jung Y et al (2020) *Caenorhabditis elegans* Lipin 1 moderates the lifespan-shortening effects of dietary glucose by maintaining ω-6 polyunsaturated fatty acids. Aging Cell. https://doi.org/10.1111/acel.13150

Kim BK, Park SK (2020) Phosphatidylserine modulates response to oxidative stress through hormesis and increases lifespan via DAF-16 in *Caenorhabditis elegans*. Biogerontology 21(2):231–244. https://doi.org/10.1007/s10522-020-09856-0

Kim Y et al (2018) Graphene oxide nano-bio interaction induces inhibition of spermatogenesis and disturbance of fatty acid metabolism in the nematode *Caenorhabditis elegans*. Toxicology 410:83–95. https://doi.org/10.1016/j.tox.2018.09.006

Kim SH et al (2019) Phosphatidylcholine extends lifespan via DAF-16 and reduces amyloid-beta-induced toxicity in *Caenorhabditis elegans*. Oxid Med Cell Longev. https://doi.org/10.1155/2019/2860642

Kyriakakis E, Charmpilas N, Tavernarakis N (2017) Differential adiponectin signalling couples ER stress with lipid metabolism to modulate ageing in *C. elegans*. Sci Rep. https://doi.org/10.1038/s41598-017-05276-2

Lanza IR et al (2012) Chronic caloric restriction preserves mitochondrial function in senescence without increasing mitochondrial biogenesis. Cell Metab 16(6):777–788. https://doi.org/10.1016/J.CMET.2012.11.003

Ledesma MD, Martin MG, Dotti CG (2011) Lipid changes in the aged brain: Effect on synaptic function and neuronal survival. Prog Lipid Res. https://doi.org/10.1016/j.plipres.2011.11.004

Lee D et al (2019) MDT-15/MED15 permits longevity at low temperature via enhancing lipidostasis and proteostasis. PLoS Biol. https://doi.org/10.1371/journal.pbio.3000415

Li Y et al (2018) C. Elegans fatty acid two-hydroxylase regulates intestinal homeostasis by affecting heptadecenoic acid production. Cell Physiol Biochem 49(3):947–960. https://doi.org/10.1159/000493226

Littlejohn NK et al (2020) A feedback loop governs the relationship between lipid metabolism and longevity. Elife 9:1–26. https://doi.org/10.7554/eLife.58815

Liu D et al (2021) Carnitine promotes recovery from oxidative stress and extends lifespan in *C. elegans*. Aging 13(1):813–830

Macedo F, Romanatto T et al (2020a) Lifespan-extending interventions enhance lipid-supported mitochondrial respiration in *Caenorhabditis elegans*. FASEB J 34(8):9972–9981. https://doi.org/10.1096/fj.201901880R

Macedo F, Martins GL et al (2020b) Lipase-like 5 enzyme controls mitochondrial activity in response to starvation in *Caenorhabditis elegans*. Biochim Biophys Acta Mol Cell Biol Lipids. https://doi.org/10.1016/j.bbalip.2019.158539

Markaki M, Tavernarakis N (2020) *Caenorhabditis elegans* as a model system for human diseases. Curr Opin Biotechnol 63:118–125. https://doi.org/10.1016/j.copbio.2019.12.011

Maulik M et al (2019) Genetic silencing of fatty acid desaturases modulates α-synuclein toxicity and neuronal loss in Parkinson-like models of *C. elegans*. Front Aging Neurosci. https://doi.org/10.3389/fnagi.2019.00207

McMurray F, Patten DA, Harper ME (2016) Reactive oxygen species and oxidative stress in obesity—recent findings and empirical approaches. Obesity. https://doi.org/10.1002/oby.21654

Möller S et al (2020) Healthspan pathway maps in *C. elegans* and humans highlight transcription, proliferation/biosynthesis and lipids. Aging. https://doi.org/10.18632/aging.103514

Murphy CT, Hu PJ (2013) Insulin/insulin-like growth factor signaling in *C. elegans*. WormBook. https://doi.org/10.1895/wormbook.1.164.1

Mutlu AS, Duffy J, Wang MC (2021) Lipid metabolism and lipid signals in aging and longevity. Dev Cell 56(10):1394–1407. https://doi.org/10.1016/J.DEVCEL.2021.03.034

Negrete-Hurtado A et al (2020) Autophagy lipidation machinery regulates axonal microtubule dynamics but is dispensable for survival of mammalian neurons. Nat Commun 11(1):1–19. https://doi.org/10.1038/s41467-020-15287-9

Park DS et al (2003) Caveolin-1 null (-/-) mice show dramatic reductions in life span. Biochemistry 42(51):15124–15131. https://doi.org/10.1021/BI0356348

Park HEH et al (2021) A PTEN variant uncouples longevity from impaired fitness in *Caenorhabditis elegans* with reduced insulin/IGF-1 signaling. Nat Commun. https://doi.org/10.1038/s41467-021-25920-w

Possik E et al (2022) Phosphoglycolate phosphatase homologs act as glycerol-3-phosphate phosphatase to control stress and healthspan in *C. elegans*. Nat Commun. https://doi.org/10.1038/s41467-021-27803-6

Pradhan A, Olsson PE, Jass J (2018) Di(2-ethylhexyl) phthalate and diethyl phthalate disrupt lipid metabolism, reduce fecundity and shortens lifespan of *Caenorhabditis elegans*. Chemosphere 190:375–382. https://doi.org/10.1016/j.chemosphere.2017.09.123

Pryor R et al (2019) Host-microbe-drug-nutrient screen identifies bacterial effectors of metformin therapy. Cell 178(6):1299-1312.e29. https://doi.org/10.1016/j.cell.2019.08.003

Qi W et al (2017) The ω-3 fatty acid α-linolenic acid extends *Caenorhabditis elegans* lifespan via NHR-49/PPARα and oxidation to oxylipins. Aging Cell 16(5):1125–1135. https://doi.org/10.1111/acel.12651

Rai N et al (2019) Metal contaminated soil leachates from an art glass factory elicit stress response, alter fatty acid metabolism and reduce lifespan in *Caenorhabditis elegans*. Sci Total Environ 651:2218–2227. https://doi.org/10.1016/j.scitotenv.2018.10.067

Ramachandran PV et al (2019) Lysosomal signaling promotes longevity by adjusting mitochondrial activity. Dev Cell 48(5):685-696.e5. https://doi.org/10.1016/j.devcel.2018.12.022

Reisner K et al (2011) Trans fat diet causes decreased brood size and shortened lifespan in *Caenorhabditis elegans* delta-6-desaturase mutant fat-3. J Biochem Mol Toxicol 25(5):269–279

Roitenberg N et al (2018) Modulation of caveolae by insulin/IGF -1 signaling regulates aging of *Caenorhabditis elegans*. EMBO Rep. https://doi.org/10.15252/embr.201745673

Schmeisser S et al (2019) Muscle-specific lipid hydrolysis prolongs lifespan through global lipidomic remodeling. Cell Rep 29(13):4540-4552.e8. https://doi.org/10.1016/j.celrep.2019.11.090

Shamitko-Klingensmith N et al (2016) Microtubule modification influences cellular response to amyloid-β exposure. AIMS Biophys 3(2):261–285. https://doi.org/10.3934/BIOPHY.2016.2.261

Shi D et al (2020) The precursor of PI(3,4,5)P3 alleviates aging by activating daf-18(Pten) and independent of daf-16. Nat Commun. https://doi.org/10.1038/s41467-020-18280-4

Sohal RS, Weindruch R (1996) Oxidative stress, caloric restriction, and aging. Science 273(5271):59–63. https://doi.org/10.1126/SCIENCE.273.5271.59

Tharyan RG et al (2020) NFYB-1 regulates mitochondrial function and longevity via lysosomal prosaposin. Nat Metab 2(5):387–396. https://doi.org/10.1038/s42255-020-0200-2

The Lancet Gastroenterology & Hepatology (2021) 'Obesity: another ongoing pandemic. Lancet Gastroenterol Hepatol. https://doi.org/10.1016/S2468-1253(21)00143-6

Thelen AM, Zoncu R (2017) Emerging roles for the lysosome in lipid metabolism. Trends Cell Biol. https://doi.org/10.1016/j.tcb.2017.07.006

Tracey TJ et al (2018) Neuronal lipid metabolism: multiple pathways driving functional outcomes in health and disease. Front Mol Neurosci 11:10. https://doi.org/10.3389/FNMOL.2018.00010/BIBTEX

Wang C et al (2017) Small-molecule TFEB pathway agonists that ameliorate metabolic syndrome in mice and extend *C. elegans* lifespan. Nat Commun. https://doi.org/10.1038/s41467-017-02332-3

Wang K et al (2018) Enhanced ROS production leads to excessive fat accumulation through DAF-16 in *Caenorhabditis elegans*. Exp Gerontol 112:20–29. https://doi.org/10.1016/j.exger.2018.07.017

Wang C et al (2019) Tris(1,3-dichloro-2-propyl) phosphate accelerated the aging process induced by the 4-hydroxynon-2-enal response to reactive oxidative species in *Caenorhabditis elegans*. Environ Pollut 246:904–913. https://doi.org/10.1016/j.envpol.2018.12.082

Wang F et al (2021) Saturated very long chain fatty acid configures glycosphingolipid for lysosome homeostasis in long-lived *C. elegans*. Nat Commun. https://doi.org/10.1038/s41467-021-25398-6

Ward CP et al (2022) Aging alters the metabolic flux signature of the ER-unfolded protein response in vivo in mice. Aging Cell. https://doi.org/10.1111/ACEL.13558

Weir HJ et al (2017) Dietary restriction and AMPK increase lifespan via mitochondrial network and peroxisome remodeling. Cell Metab 26(6):884-896.e5. https://doi.org/10.1016/j.cmet.2017.09.024

Welsh CE, Matthews FE, Jagger C (2021) Trends in life expectancy and healthy life years at birth and age 65 in the UK, 2008–2016, and other countries of the EU28: an observational cross-sectional study. Lancet Reg Health. https://doi.org/10.1016/j.lanepe.2020.100023

Wu D et al (2020) Inhibition of PAR-1 delays aging via activating AMPK in *C. elegans*. Aging 12(24):25700–25717

Wymann MP, Schneiter R (2008) Lipid signalling in disease. Nat Rev Mol Cell Biol. https://doi.org/10.1038/nrm2335

Xu A et al (2019) Microtubule regulators act in the nervous system to modulate fat metabolism and longevity through DAF-16 in *C. elegans*. Aging Cell. https://doi.org/10.1111/acel.12884

Yang L et al (2020) Neuronal lipolysis participates in PUFA-mediated neural function and neurodegeneration. EMBO Rep. https://doi.org/10.15252/embr.202050214

Zečić A, Braeckman BP (2020) DAF-16/FoxO in *Caenorhabditis elegans* and its role in metabolic remodeling. Cells. https://doi.org/10.3390/cells9010109

Zhang S et al (2017) NCEH-1 modulates cholesterol metabolism and protects against α-synuclein toxicity in a *C. elegans* model of Parkinson's disease. Hum Mol Genet 26(19):3823–3836. https://doi.org/10.1093/hmg/ddx269

Zhao YY et al (2002) Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice. Proc Natl Acad Sci USA 99(17):11375. https://doi.org/10.1073/PNAS.172360799