Chemistry and Physics of Lipids 222 (2019) 59–69

Contents lists available at ScienceDirect

Chemistry and Physics of Lipids

journal homepage: www.elsevier.com/locate/chemphyslip

Review

The role of lipids in aging-related metabolic changes

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ARTICLE INFO

Keywords:
Aging
Mass spectrometry
Odd chain fatty acids
Oxidized lipids
Vinyl-Ether lipids
Polyunsaturated fatty acids

ABSTRACT

Fat is historically associated with poor health and obesity. However, the continuous use of lipidomics and genetic studies in model organisms revealed that specific lipid profiles and signals might delay aging. In order to identify and quantify the lipid species, researchers are taking advantage of the recent developments in the area of lipidomics that is mainly done by mass spectrometry and further techniques, such as NMR spectroscopy and chromatographic separations.

This review will emphasize the role of lipid composition and metabolism during aging. We review the molecular and physiological changes during the progression of aging with a special focus on the role of lipids. Interventions to modulate life span in a variety of organisms such caloric restriction, show a significant extension of their maximum life-span and a decrease in the onset of age-related diseases. In particular, the influence of dietary restriction in lipid metabolism will be a major point of this review.

1. Introduction

Biological aging is a universal process characterized by a progressive deterioration of tissue structure and function (Balcombe and Sinclair, 2001), which increases the risk of developing multiple chronic conditions such as cancer, cardiovascular, metabolic, neurodegenerative and autoimmune diseases, leading finally to death (Burkle et al., 2007; Stepanova et al., 2015).

Why and how do we age is still an open question. A wide number of theories have been proposed over the past decades (Medvedev, 1990), ranging from the accumulation of damage to the biological programmed aging. It is widely accepted, however, that theories from both categories are not necessarily exclusive, and aging is regarded as a complex, multifactorial process driven by both intrinsic (genetic) and extrinsic (environmental) factors (Balcombe and Sinclair, 2001; Medvedev, 1990).

Recent reviews of the aging process integrate many different theories in a global perspective. An interesting example is the work by López-Otín et al. (Lopez-Otin et al., 2013), which describes the etiology and progression of senescence by proposing 9 universal hallmarks. These are, in turn, classified into three categories according to their role during the aging process: primary, antagonistic and integrative hallmarks, which will be further discussed in the following section. However, because they are highly interconnected (Lopez-Otin et al., 2016), a major goal is to dissect such connectivity and understand their relative contributions to senescence.

This review will focus on the role of lipids composition and metabolism during aging, as recent research reveals a connection between lipid profiles and longevity (Bustos and Partridge, 2017; Schroeder and Brunet, 2015). Although fat is historically associated with poor health and obesity (Naude et al., 2018) specific lipid profiles and signals may delay aging as shown in recent studies with mice (Newman et al., 2017). The continuous use of lipidomics and genetic studies of lipid synthesis and signaling pathways is likely to reveal many new roles for lipids in the regulation of longevity and increase our understanding of the complex relationship between lipids and aging.

Here, we will first introduce the molecular and physiological changes during aging with a special focus on the role of lipids. We will then discuss the influence of dietary restriction in lipid metabolism, recent advances in lipidomics research and, finally, changes in lipid profiles and lipid signaling pathways during aging and age-related diseases.

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https://doi.org/10.1016/j.chemphyslip.2019.05.005
Received 19 February 2019; Received in revised form 22 May 2019; Accepted 28 May 2019
Available online 29 May 2019
0009-3084/

2. Theories of aging and molecular, physiological & pathophysiological changes with aging

2.1. Primary hallmarks

According to a recent review (Lopez-Otin et al., 2013), primary hallmarks are the primary causes of damage, intrinsically negative and accumulative. Previous theories of senescence fall into this category, such as the accumulation of random genome damage throughout life (genomic instability) (Moskalev et al., 2013), the progressive loss of telomeres (Blasco, 2007), epigenetic alterations (Peleg et al., 2016b) and loss of proteostasis (Labbadia and Morimoto, 2015).

Of special interest is the accumulated damage of the mitochondrial DNA (mtDNA) during aging (Wei et al., 2009). Mitochondria are the primary source of reactive oxygen species (ROS), so they are especially susceptible to ROS damage at the mtDNA, membrane lipids (peroxidation) and proteins of the respiratory chain. For instance, cardiolipin levels in the mitochondrial membrane are imbalanced in human senescent cells (Maftah et al., 1994; Chicco and Sparagna, 2007), which triggers genome instability and alterations in the stress response signalling (Zhou et al., 2009). Such genomic damage results in further ROS overproduction and creates a vicious cycle that leads to mitochondrial dysfunction, tissue damage and cell death (Wei et al., 2009). In addition, there is a close relationship between mitochondrial dysfunction and changes in metabolism during aging, such as the decline in NAD^+ levels in worms (Mouchiroud et al., 2013), rodents (Braidy et al., 2011) and humans (Massudi et al., 2012) partially due to ROS overproduction and the altered redox state of the mitochondria.

Accordingly, lipid homeostasis is imbalanced during aging from worms to humans. This occurs not only due to mitochondrial dysfunction but also by epigenetic alterations that modify gene expression (Ahuja et al., 2019; Papsdorf and Brunet, 2019), so there is a bidirectional cross-talk between nutrient sensing pathways and epigenetics. For example, lipids are able to directly alter the epigenetic landscape via Acetyl-CoA (a degradation product of fatty acid oxidation) which is used for histone acetylation (Ahuja et al., 2019; Imhof and Peleg, 2016; Peleg et al., 2016a, b; Brunet and Rando, 2017; Quiros et al., 2016); while the epigenetic alterations can, in turn, modulate lipid metabolism and distribution (Peleg et al., 2016b; Brunet and Rando, 2017; Quiros et al., 2016). Almost all enzymes that modify chromatin use metabolites from core metabolic pathways as substrates or co-factors, such as Acetyl-CoA, nicotinamide adenine dinucleotide (NAD^+), flavin adenine dinucleotide (FAD), ATP or S-adenosylmethionine (SAM), uridine diphosphate (UDP)-glucose, and α-ketoglutarate (α-KG) (Gut and Verdin, 2013; Lu and Thompson, 2012). Such metabolites inform about the metabolic status of the cell and are sensed by chromatin-modifier enzymes. An interesting example of metabolic sensors which is gaining much attention in the scientific community are sirtuins, histone deacetylases (HDACs) that sense the intracellular NAD^+ levels, which reflect the energetic state of the cell (Houtkooper et al., 2012; Bonkowski and Sinclair, 2016).

In mammals, sirtuins are a family of 7 proteins, from SIRT1 to SIRT7, and their activity is enhanced upon nutrient-stress conditions when NAD^+ levels increase (Canto and Auwerx, 2012). Indeed, it has been suggested that the beneficial effects of dietary restriction depend on NAD^+ sensing by SIRT1 (Lu and Lin, 2010; Guarente, 2013). Aging and age-related diseases also benefit from SIRT1 activation: resveratrol stimulates SIRT1 activity, improves mitochondrial function (Lagouge et al., 2006) and extends lifespan in mice ((Baur et al., 2006; Minor et al., 2011), although this only occurs when the animals are metabolically stressed (i.e. fed with a high-fat diet) (Baur et al., 2006; Minor et al., 2011). Thus, it has been recently hypothesized that sirtuins do not play a direct role in aging but instead activate stress-response pathways, which are involved in health and lifespan (Canto and Auwerx, 2012).

2.2. Antagonistic hallmarks

While primary damage accumulates throughout time, the antagonistic hallmarks are triggered as a homeostatic process that compensates the damage. Such compensatory mechanisms are, at first, favorable for cell survival; but they eventually become detrimental and promote an aging phenotype (Lopez-Otin et al., 2013). A common example is the generation of ROS, which show beneficial physiological roles at moderate concentrations (Valko et al., 2007; Schieber and Chandel, 2014; Droge, 2002) but can also lead to mitochondrial dysfunction and excessive oxidative damage if they are not balanced (Droge, 2002; Hekimi et al., 2011). Lipid peroxidation occurs when fats, especially polyunsaturated fatty acids (PUFAs), are attacked by ROS, and this process plays an important role in cellular aging (Ayala et al., 2014; Arguelles et al., 2014). In response to lipid peroxidation, pancreatic beta cells upregulate the antioxidant machinery and other signalling pathways involved in damage repair and survival (Maulucci et al., 2016). However, under high levels of peroxidation and oxidative stress, cells induce apoptosis.

Another compensatory mechanism is the dysregulation of nutrient sensing pathways, especially the insulin and Insulin-like growth factor (IGF)-1 signaling (IIS) pathway (Riera and Dillin, 2015; Bettedi and Foukas, 2017). Several studies show that decreased activity of the IIS extends lifespan in many different model organisms (Kenyon, 2011; Selman et al., 2011; Nelson et al., 2012; Altintas et al., 2016; Templeman et al., 2017) but, paradoxically, studies with mice indicate that the IIS also declines during normal aging (Schumacher et al., 2008). Moreover, it has recently been observed that metabolic alterations during aging follow a biphasic curve, where metabolic activity increases during middle-age and declines again later in life (Baker and Peleg, 2017). Thus, IIS down-regulation in middle age can be interpreted as a defensive response to systemic damage, aimed at slowing down cell metabolism in order to reduce the rate of cellular damage and survive longer.

Of interest is the role of the IIS pathway in modulating the metabolism of lipids. Activation of the downstream factor FOXO (Forkhead box O), a family of transcription factors highly conserved from Cahenorhabditis elegans to mammals, increases lifespan (Martins et al., 2016). Interestingly, in C.elegans the FOXO ortholog DAF-16 promotes lipid degradation and synthesis of mono-unsaturated fatty acids (MUFAs) (Murphy et al., 2003). As PUFAs oxidize more rapidly than MUFAs, a higher MUFA/PUFA ratio is associated with an increased lifespan (Papsdorf and Brunet, 2018). Consistent with this, PUFAs increase during aging but are lower in long-lived mice (Papsdorf and Brunet, 2019).

The mechanistic target of rapamycin (mTOR) is also a critical player that affects aging by regulating lipid homeostasis in response to nutrient availability (Caron et al., 2015; Lamming and Sabatini, 2013). mTOR is a kinase well conserved from yeast to mammals, found in two complexes named mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which regulate cell growth and metabolism. Activation of both complexes in response to specific nutrients (i.e. aminoacids) and growth factors (i.e. insulin), promotes energy conservation by lipid storage (adipogenesis and lipogenesis) and triggers the shut down of catabolic processes such as autophagy, lipolysis and β-oxidation (Soliman, 2011).

It is well documented that the TOR pathway mediates, at least in part, the protective effects of dietary restriction (Garratt et al., 2016). mTOR suppression triggers stress-response pathways which are linked to longevity, like autophagy, heat resistance, antioxidant responses, cell-cycle control and homeostasis (Aramburu et al., 2014). Inhibition of mTORC1 with rapamycin or genetic interventions also extends lifespan in many model organisms (Harrison et al., 2009; Johnson et al., 2013).

Another antagonistic hallmark is cellular senescence (Lopez-Otin et al., 2013), which is regarded as a tumor suppressor mechanism in

one hand by inhibiting proliferation of damaged, aged cells; but which also promotes a senescent associated secretory phenotype (SASP) in which cells secrete a series of cytokines, chemokines and growth factors to their surroundings, prompting other cells to become senescence and creating a pro-inflammatory environment, eventually favorable for tumor development (Coppe et al., 2010; Velarde et al., 2013). Indeed, new work has shown several health benefits of clearing senescence cells in mice (Baker et al., 2011, 2016).

Remarkably, senescent cells are characterized by having a stiffer membrane (Matjusaitis et al., 2016). Membrane fluidity decreases in brain, liver and heart in aging rats (Hulbert et al., 2007) due to an altered lipid composition. Indeed, membrane sphingolipids can promote either cell proliferation - when they are converted into sphingosine-1-phosphhatase (SP1) - or apoptosis -when they are converted into ceramides (Papsdorf and Brunet, 2019). An imbalance of the S1P/ceramide axis is associated with aging and age-related diseases like diabetes, as it shows an important role in the regulation of energy balance in rodents (Green et al., 2017). Moreover, SP1 is involved in multiple cellular signaling processes like immune cell trafficking. As such, it has been implicated in inflammatory disorders like diabetes, atherosclerosis and cancer (Spiegel and Milstien, 2011; Kunkel et al., 2013).

2.3. Integrative hallmarks

According to Lopez-Otin et al. (2013) model, the integrative hallmarks eventually arise when homeostatic mechanisms are not sufficient to compensate the damage, leading to stem cell exhaustion and altered intercellular communication. Both of these lead to an increased risk of multimorbidity and the final aging phenotype.

Importantly, many different types of damage can trigger the same phenotype. For instance, telomere shortening, DNA damage and oncogene overexpression, can all trigger cell cycle arrest and senescence, with stem cell exhaustion as a common end-point. Such a consequence impairs the regenerative capacity of tissues and triggers age-related conditions like osteoporosis and sarcopenia in old mammals (Conboy and Rando, 2012).

Similarly, stem cell exhaustion at the hematopoietic system contributes to maintain a senescent immune system. A permanent low-grade inflammation is an important biomarker of aging, and a common denominator of several age-related diseases (Shaw et al., 2010). Interestingly, studies with humans and animals reveal that the lipid composition and the distribution of lipid rafts is altered in aged T-lymphocytes (Fulop et al., 2012). Lipid rafts become less fluid and dynamic when cholesterol content increases in aged T-cells, drastically altering the T-cell activation signaling cascades (Fulop et al., 2012).

Another example of altered intercellular communication is that human adipose tissue secretory profiles change with age (Gonzalez-Covarrubias, 2013). Fat storage and plasma triglyceride levels are also elevated, which increase the risk of developing age-related conditions like diabetes, cardiovascular and metabolic diseases. Notably, the cellular uptake of serum triglycerides seems to have a protective effect in C. elegans, especially if they are enriched in MUFAs (Papsdorf and Brunet, 2018). Fat remodeling effects like lipid accumulation in somatic cells, fatty acid desaturation, lipolysis and autophagy has also been reported in C. elegans after germline removal (Hansen et al., 2013), thus suggesting that lipid metabolism may have an important role in switching between somatic maintenance and reproduction.

Germ line removal is, indeed, a mechanism that significantly increases lifespan in worms (Hsin and Kenyon, 1999; Arantes-Oliveira et al., 2002) and flies (Flatt et al., 2008), although much work has been focused on C. elegans and studies with flies have been controversial so far (Barnes et al., 2006). Work with C. elegans shows that lifespan extension through germ-cell loss is dependent on DAF-16 (Berman and Kenyon, 2006), therefore directly linked to the IIS pathway, which regulates energy balance and lifespan. Of interest, the link between reproduction and the IIS pathway can be seen also in mammals: many studies show a decrease in fertility after reducing the IIS or during caloric restriction (Weindruch et al., 1986; Bruning et al., 2000; Burks et al., 2000; Zaczek et al., 2002; Partridge et al., 2005; Martin et al., 2008; Ghazi, 2013; Maklakov and Immler, 2016), probably due to the interconnectivity between nutrient sensing pathways and the neuroendocrine control of the reproductive system (Zieba et al., 2005; Uhlenhaut and Treier, 2011). It seems therefore that the germline regulation of lifespan might be conserved through evolution, although its molecular and physiological mechanisms are poorly understood.

3. Delaying aging by caloric restrictions and effects on lipid metabolism

From yeast to primates, calorically restricted animals show an extension of their maximum life-span and a decrease in the onset of age-related diseases (Fontana and Partridge, 2015; Puca et al., 2008; Clancy et al., 2002; Mattison et al., 2017). Despite being one of the most studied intervention for delaying aging, the underlying molecular and cellular mechanisms of caloric restriction (CR) are still not well understood (Di Francesco et al., 2018). Several hypotheses have been suggested, such as the reduction of metabolic rate (with no supporting evidence nowadays) (Masoro, 2005), reduction of oxidative damage (Mattson et al., 2014) and attenuation of the IIS pathway (Fontana et al., 2010), among others, which are not necessarily exclusive.

Interestingly, it has been suggested that such theories are just mere examples of hormetic processes (Rattan, 2008; Masoro, 2005), so CR can be regarded as a small stressor that triggers upregulation of pathways for maintenance and repair in a pleiotropic way, with the IIS pathway, mTOR, FOXO, AMP-aktivierte Proteinkinase (AMPK), heat shock factor (HSF) protein and sirtuins involved (Fontana and Partridge, 2015). For instance, CR increases the formation of free radicals within the mitochondria, which causes a secondary induction of antioxidant defenses, a clear example of hormesis (Ristow and Schmeisser, 2014; Shimokawa and Trindade, 2010). Similarly, autophagy, an evolutionary conserved process that degrades cellular components in response to starvation, is very much associated with health and longevity, and it's induced during CR (Longatti et al., 2012).

Regarding the relationship between CR and lipid metabolism, it is noteworthy that CR delays age-related DNA methylation in mammals, including primates (Maegawa et al., 2017, Hahn et al., 2017, de Magalhaes and Church, 2005) affecting genes involved in lipid metabolism and finally leading to higher lipolysis and shorter fatty acid chain lengths (Hahn et al., 2017). In addition, lipid homeostasis is fundamental for regulation of autophagy, since deletion of enzymes responsible for triglycerides (TG) and sterol esters completely blocks starvation-induced autophagy in yeast cells (Velazquez et al., 2016). Indeed, lipids play an essential role not only at regulating autophagy-related genes but also at the level of membrane components (Bustos and Partridge, 2017).

In humans, long term caloric restriction (CR) influences the same biological parameters that are altered with aging (Anderson and Weindruch, 2010; Most et al., 2017). These include risk factors for atherosclerosis, such as reduction of serum total cholesterol, low density lipoprotein cholesterol (LDL), TG, fasting glucose and insulin, high sensitivity C-reactive protein, systolic and diastolic pressure, while other factors like high density lipoprotein (HDL) are increased (Fontana et al., 2004). Changes in adipose tissue secreted systemic factors like adipokines are also altered (Miller et al., 2017; Zhu et al., 2004). Adiponectin levels strongly increase in CR animals, which is accompanied by a reduction of plasma and tissue TGs, and an improvement of insulin sensitivity (Zhu et al., 2004).

Other protective effects in calorically restricted versus ad libitum rats include a decrease of lipid peroxidability and maintenance of membrane fluidity (Yu et al., 1992). Changes in lipid membrane bilayer profiles (decrease in the C20:4n-6/C18:2n-6 ratio) that occur under CR are associated with reduced peroxidability (Laganiere and Yu, 1993;

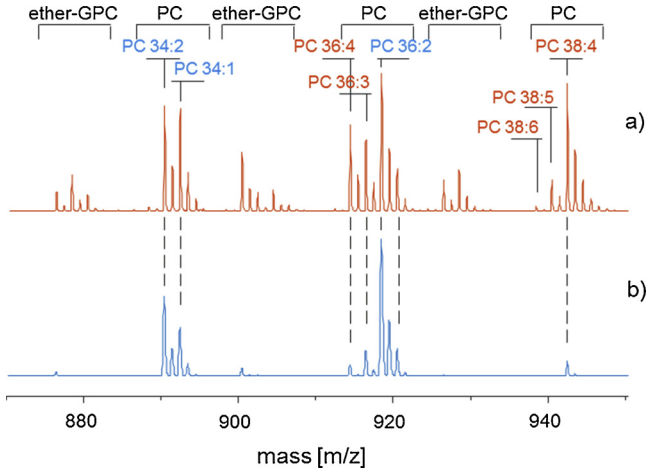

Fig. 1. Lipid profiles of FDCPmix cells cultivated under a) normal glucose content and b) low glucose starvation measured by MALDI-TOF mass spectrometry in the positive ion mode after organic extraction and is reproduced with modifications and permission from Elsevier (Fuchs et al., 2011a,b). The PC species containing 3 or more double bonds (PUFA) decreases drastically in comparison to PC species with 2 or 1 double bonds under glucose deprivation. Further, the ether-linked lipid species decrease as well almost entirely. Abbreviations: GPC, glycerophosphocholine; PC, phosphatidylcholine.

Hulbert, 2005). As demonstrated in Fig. 1, under low glucose starvation the lipid membrane bilayer profile of cultured FDCPmix cells shifts drastically to a decreased PC 36:4/PC 36:2 ratio (Fuchs et al., 2011a). High membrane fluidity and low membrane peroxidability are the optimal membrane conditions for promoting longevity (Puca et al., 2008). This theory has been generated from the observation that body mass/maximum life span in mammal and bird species correlates directly and inversely with the membrane levels of C18:1 n-9 and C22:6 n-3, respectively. This can be explained by the fact that the latter one is 320-fold more susceptible than C18:1 n-9 to peroxidation, while they both have good fluidity properties (Hulbert, 2005).

In mice, CR also promotes longevity via induction of endothelial nitric oxide synthase (e-nos) expression (which exerts cardiovascular protection), mitochondrial biogenesis and ATP production. These effects are strongly reduced in e-nos null mutant mice (Nisoli et al., 2005), although this work was later challenged (Hancock et al., 2011). Still, there is evidence that the molecular stressor $NO^{\bullet}$, an e-nos product that induces trans-fatty acids formation (Kermorvant-Duchemin et al., 2005), plays a role in CR. One possibility is that in wild-type CR animals $NO^{\bullet}$, acting via mitochondrial biogenesis, increases ß-oxidation and lipolysis. This may result in reduced accumulation of fat and an increased lifespan (Nisoli et al., 2005).

CR is perhaps the most studied intervention that effectively delays the onset of age-related diseases and extends lifespan. However, bringing this therapy to society has major drawbacks. As the typical CR regimen entails a 20–40% decrease in calories, most individuals find it difficult to sustain such a diet over time. Moreover, CR requires careful planning and appropriate patient counseling, as associated concerns with long-term CR include an increased risk of osteoporosis, fatigue and loss of muscle mass (Lipsky and King, 2015). Other regimes such as intermittent fasting or macronutrient restrictions without calorie deficit have proved to be a more feasible and safe intervention, equally powerful as CR (Greer and Brunet, 2009); Mattson et al., 2014; (Lee and Longo, 2016). For instance, recent studies show that restriction of protein or specific amino acids (i.e. methionine and tryptophan) also extends health and lifespan in various animal models (Mirzaei et al., 2014). Recent reports also support the notion that a low carbohydrate, fat-based diet -ketogenic diet- is beneficial for increased healthy life span (Newman et al., 2017; Roberts et al., 2017). In addition, drugs that mimic the CR effects have also great potential and may be better translated to society. Examples that are being investigated are Metformin, a drug for diabetes which targets insulin metabolism (Anisimov, 2013), Rapamycin, which interacts with mTOR signaling and affects autophagy (Blagosklonny, 2012), and Resveratrol, which interferes with sirtuin activity (Gertz et al., 2012).

In summary, understanding how lipid content and composition is altered during aging may offer novel insight as to how various hallmarks of aging are changed. As the analysis of lipids is rather complex, various mass spectrometry-based techniques have emerged. Next, we discuss such technologies and methods to characterize lipidomics and how novel lipidomics data enable novel insights into aging.

4. Technological advances in –omics research, mass spectrometric methods in lipidomics research

The first step in the lipidomics analyses is the two phase extraction of the lipid species done in most cases by the Bligh & Dyer or Folch method (Bligh and Dyer, 1959; Folch et al., 1957). The obtained lower chloroform layer of the organic extraction can be used for further analysis without the necessity of further purification. In Fig. 2 the typical workflow for lipid analysis and several selected techniques are shown. This table provides a very general overview of various methods and the underlying principles as well as the corresponding advantages and disadvantages. The methods can be grouped into techniques based on chromatography, mass spectrometry (MS) and other spectroscopic techniques. In order to obtain the maximum of information, it is advisable to combine two or more techniques, such as liquid chromatography (LC)-MS and gas chromatography (GC)-MS.

Modern lipid analysis approaches are normally done by MS (Want et al., 2005) and typically preceded by LC separation (Sommer et al., 2006; Zhao et al., 2014) or GC (A et al., 2005; Kohler et al., 2016; Jurowski et al., 2017). The dynamic range for lipid analyses has been

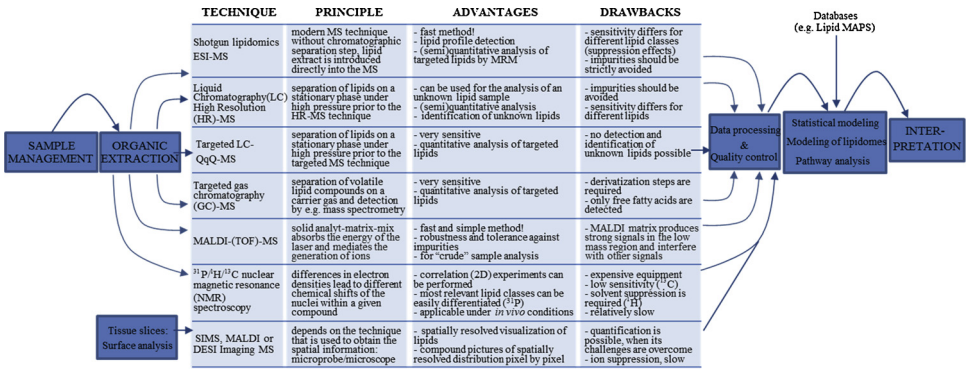

Fig. 2. Typical workflow of lipid analysis (left to right). Abbreviations: DESI, desorption electrospray ionization; ESI, electrospray ionization; MALDI, matrix-assisted laser desorption/ionization; QqQ, triple quadrupole; SIMS; secondary ion mass spectrometry.

affectedly extended that it is nowadays possible to identify and quantify lipid classes of very low concentrations (e.g., lysophospholipids, ceramide, sphingosine-1-phosphate) (Han et al., 2005; Farwanah et al., 2011) and/or achieve analysis of very low-abundant molecular species in many lipid classes (e.g. phosphatidylinositols, cardiolipins and ether lipids) (Han et al., 2006; Tyurina et al., 2014). New MS-based lipidomics methods allow the study of intact lipid molecules from very small amounts of extracted samples (Han and Gross, 2005; Schwudke et al., 2006).

Lipidomics has made fast progress on various fronts over the past years although it still needs to achieve the same level of advancement and knowledge as genomics and proteomics. The challenge is the diversity of lipid species for both the experimental and the informatics positions. There is the need for a robust bioinformatics infrastructure for the (a) establishment of a globally accepted classification system, creation of databases of lipid structures, lipid related genes and proteins (done by the initiative of the LIPID MAPS consortium); (b) efficient analysis of experimental data; (c) integration of experimental data and existing knowledge into metabolic and signaling pathways; and (d) development of software for efficient search, display, and analysis of lipidomic data, among others (Naudi et al., 2015).

Characterizing lipids presents unique challenges, but new technologies facilitate quantitative detection of diverse lipids in human samples and model organisms typically used in aging studies (Schroeder and Brunet, 2015). Current methods utilizing LC–MS can detect a great variety of unique lipid species, including novel lipid molecules (Brugger, 2014). Although it is still not possible to detect all types of lipid molecules in one sample, LC–MS-based methods combined with sophisticated software to aid in lipid identification can detect hundreds of distinct lipids. Other methods that degrade lipids into its chain components can detect differences in FA structure at high resolution, revealing trends in lipid profiles (Li et al., 2014; Brugger, 2014). Analysis of metabolites without specifically targeting lipids can also identify some new lipid molecule species (Folick et al., 2015b).

Lipidomics requires specific solutions for analysis, data handling and lipid pathway analysis because of the huge diversity of lipids (Yetukuri et al., 2008; Tumanov and Kamphorst, 2017). Fig. 2 gives an outline of different steps of a lipidomics platform. The first decision before performing lipidomics analyses is to define the number of lipid species of interest. For a defined set of metabolites a targeted approach should be selected or an untargeted approach should be chosen if the goal of the experiment is entire lipidome determination (Patti et al., 2012; Cajka and Fiehn, 2016).

However, no single extraction method is capable to extract all lipid classes from a biological matrix with good efficiency because lipids are very heterogeneous and complex molecules. Hence, an important step in any lipidomics analysis is the choice of the lipid extraction method that depends on the experiment objective and the targeted lipid classes (Pellegrino et al., 2014).

The second decision in the lipidomics analyses workflow is the detection of the extracted lipid species. Mass spectrometry and nuclear magnetic resonance (NMR) have become powerful tools for lipid characterization (Fuchs, 2015). It is called liquid chromatography MS (LC−MS) when the extract is introduced into MS after chromatographic separation by LC (Laaksonen et al., 2006; Zhao et al., 2014) or “shotgun lipidomics” if the lipid extract is introduced directly into the mass spectrometer (Schwudke et al., 2006; Wang et al., 2016). Beside LC, other frequently used separation tools for analysis of lipids in complex samples are thin-layer chromatography (TLC) and GC (Fuchs et al., 2015; Jurowski et al., 2017). As TLC uses a solid phase for separation, direct TLC coupling to MALDI-MS is possible (Fuchs, 2012). Additionally, MALDI-based lipid visualization can provide imaging resolution (Amoscato et al., 2014; Luberto et al., 2019; Ellis et al., 2013).

In untargeted lipidomics methodologies the most common ionization technique is electrospray ionization (ESI), but also matrix-assisted laser desorption ionization (MALDI), which are both soft ionization methods (Yang and Han, 2016). ESI (and also MALDI) can be combined with several types of mass analyzers such as time-of-flight (TOF), Orbitrap®, triple quadrupole (QqQ), and ion trap. The latter two ionization techniques are usually used for targeted approaches and the first two for untargeted experiments. Positive ion mode ESI (ESI +) allows the detection of diverse lipid classes such as major glycerolipids (GL), glycerophospholipids (GP), and sphingolipids (SP). Nevertheless, for some lipid classes such as phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylinositol (PI), free fatty acids, and carboxylate anions of the fatty acids only the negative ion mode (ESI-) can provide useful information (Seppanen-Laakso and Oresic, 2009; Watson, 2006). For specific lipid classes (such as steroids) are more sensitive ionization techniques available, for example atmospheric pressure chemical ionization or chemical ionization (Gross, 2017).

5. Changes in (glycerophospho)lipids, fatty acids, vinyl-ether lipids (plasmalogens) and oxidized lipids in aging & age related diseases

5.1. Lipid peroxidation

Total lipids extracted from plasma or isolated from erythrocyte membranes of children of long-lived individuals (nonagenarians or centenarians) contain a higher MUFA/PUFA ratio, relative to matched controls (Gonzalez-Covarrubias, 2013). As already commented, an increased MUFA/PUFA ratio may influence lifespan by reducing oxidative stress and damage (Han et al., 2017). PUFAs are most susceptible to oxidation, and oxidation of fatty acids (FAs) propagates further free radical production, thus high levels of PUFAs could increase oxidative damage (Shmookler Reis et al., 2011). There are other findings that support a link between PUFA synthesis, oxidative damage, and aging: comparing several long-lived mutants in C. elegans, the longest-lived mutants have the highest MUFA/PUFA ratios (Shmookler Reis et al., 2011). Also, higher levels of Δ9 desaturase that converts saturated FAs to MUFAs are found in long lived worms.

The oxidative stress theory of aging includes polyunsaturated lipids that are particularly susceptible to the ROS attack, whereby saturated and monounsaturated fatty acyl chains (SFA and MUFA) are essentially resistant to peroxidation (Gonzalez-Covarrubias, 2013). Moreover, oxidized lipids are able to damage other macromolecules or form adducts because they are radicals itself (Hulbert, 2003). The resulting products are mutagenic and carcinogenic, so this might contribute to the onset of age-related diseases and aging (Muller et al., 2007).

Investigations have shown that a higher MUFA/PUFA ratio is associated with lower peroxidation, oxidative damage and maximum lifespan in different tissues and animal species (Hulbert, 2005; Portero-Otin et al., 2001; Pamplona et al., 2000b, a). High levels of PUFA, such as arachidonic acid, may cause myocardial injury by induction of systemic inflammation with subsequent development of cardiovascular disease (Halade et al., 2016). PUFAs, as well as other specific FAs, might change differently in different lipid classes, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and triacylglycerol (TAG) class species (Fuchs et al., 2011b).

The susceptibility of individual FA to peroxidation is known to increase exponentially with increasing number of double bonds on carbon chains. This allows the calculation of a value that is referred as the peroxidation index (Munro and Blier, 2012). Munro and Blier (2012) found that the extreme longevity of Arctica islandica (maximum reported life time = 507 years) is associated with increased peroxidation resistance. The mitochondrial membrane peroxidation index was found to have an exponential decrease with increasing longevity among species, whereby the peroxidation index of other cell membranes showed a linear decrease. This suggests that an increase in longevity primarily results from decreasing lipid peroxidation in the mitochondrial environment. The significantly lower peroxidation index and elevated levels of plasmalogens found for A. islandica mitochondria should be a

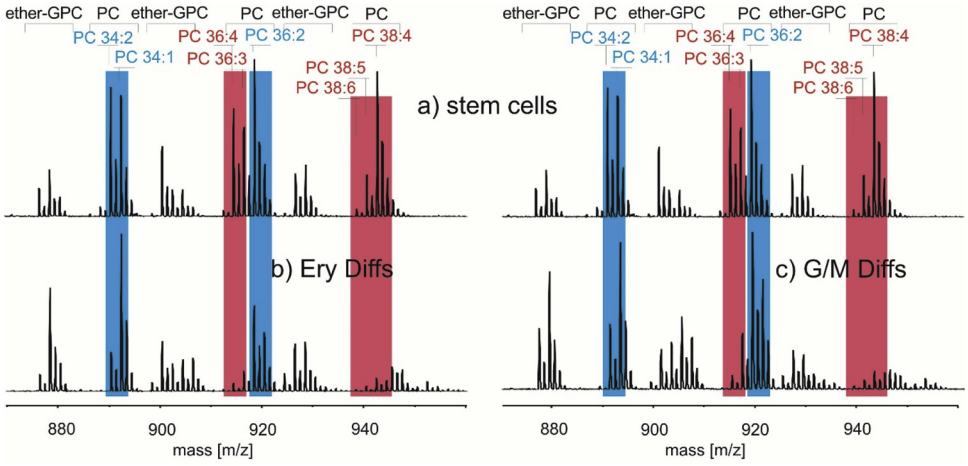

Fig. 3. Lipid profiles of FDCPmix cells cultivated under a) self-renewal conditions, b) erythropoietin and c) granulocyte-colony stimulating factor (G-CSF) measured by MALDI-TOF mass spectrometry in the positive ion mode after organic extraction. Further details about FDCP mix murine progenitor cells can be found in (Ditz et al., 2018; Fuchs et al., 2011a). The PC species containing 3 or more double bonds (PUFA) decreases drastically in comparison to PC species with 2 or 1 double bonds during erythroid differentiation (Ery Diffs) (b) and myeloid differentiation (G/M Diffs) (c). The ether-linked lipid species increase. Abbreviations: GPC, glycerophosphocholine; PC, phosphatidylcholine.

prime factor contributing to this species' extraordinary longevity.

5.2. (Vinyl)-Ether lipids - Plasmalogens

After birth and during growth, a major increase in brain weight occurs and the plasmalogen content more than doubles in developing brain (Erickson and Lands, 1959; Farooqui and Horrocks, 2001). Changes of plasmalogen lipids in endothelial phenotype cells generated from human induced pluripotent stem cells were investigated by reverse-phase ultrahigh-pressure liquid chromatography mass spectrometry analysis. The levels of plasmalogen phosphatidylethanolamines (38:5) and (38:4) increased during differentiation of endothelial cells (Nakamura et al., 2017). This increase could be also shown during differentiation of hemopoietic (murine) stem cells (Fuchs et al., 2011a,b) (as shown in Fig. 3). However, such plasmalogen gradually declines starting from 30 years old in normal human brain during aging (Rouser and Yamamoto, 1968; Lessig and Fuchs, 2009). Indeed, an 80 year old person reaches the actual plasmalogen content value of a one year old child. Other studies also show a decreased plasmalogen concentration with age (Brosche and Platt, 1998; Maeba et al., 2007). The decreasing plasmalogen content in the aging brain is associated with an increasing ratio of plasmalogen epoxide to native plasmalogen, suggesting a potential role of lipid peroxidation (Weisser et al., 1997; Braverman and Moser, 2012).

In (Yamazaki et al., 2014), age-related diseases were investigated and the serum levels of different human subjects quantified by a ^{125}I-HPLC method and characterized by LC–MS/MS. Oxidized products of plasmalogens, free aldehydes and α-hydroxyaldehydes accumulate at 30-times higher concentrations in aged brains, indicating an increased turnover of plasmalogens, their increased hydrolysis and a more significant extent of oxidation reactions (Weisser and Spiteller, 1996; Dean and Lodhi, 2018). Nevertheless, the mild stress that occurs during normal aging can be nearly completely tolerated by the up-regulation of the antioxidant defense systems, such as tocopherols and ascorbic acid, which are able to restore the oxidative balance (Farooqui and Horrocks, 2001).

The review of (Gonzalez-Covarrubias, 2013) gave an overview about lipidomic profiles associated with familial longevity on one hand and lipid species associated with risk of type 2 diabetes on the other. Particularly, an increase of specific ether-linked phosphatidylcholine and sphingomyelin species seems to be involved in lowering the risk of type 2 diabetes and finally increase longevity. Similarly, (Kawanishi et al., 2018) found that serum levels of specific ether-linked PC and phosphatidylethanolamine (PE) molecular species (e.g., PC O-36:4 and PE O-36:5) were lower in old than in young individuals. Thus, decreased ether-linked phospholipids (PL) species could be a hallmark of aging and aging-related diseases. Indeed, they are generally called "free radical scavengers" and exhibit protective effects on other molecular species, cells and tissues, by mitigating oxidative stress (Dean and Lodhi, 2018). This might be because ether-linked PLs contain a long chain fatty alcohol in the sn-1 position of the glycerol backbone instead of the fatty acyl chain (Lessig and Fuchs, 2009; Braverman and Moser, 2012). However, in contrast to vinyl-ether PLs (plasmalogens) that are modified by plasmenyl-desaturase in sn-1 position, unmodified ether-linked lipids are very stable and not susceptible to oxidative stress. Only the additional double bond, after the further desaturase step, makes plasmalogens very susceptible to oxidative stress and therefore able to act as scavenger molecules. Although it is possible to distinguish vinyl-ether PLs (plasmalogens) from ether-PLs in lipidomics analysis (Lessig and Fuchs, 2009), their identity remains uncertain in some studies because e.g. PE-O 36:5 and PE-P 36:4 (plasmalogen) are isomers.

5.3. Saturation of fatty acids

Deregulation of the stem cell niche is regarded as one of the reasons for tissue degeneration and aging. In Fig. 3 the lipid profile of hemopoietic (murine) stem cells (Fuchs et al., 2011a) are shown and compared with the lipid profile after their differentiation into erythrocytes and granulocytes/monocytes (Ditz et al., 2018). In both blood cell types, the PC species containing 3 or more double bonds (PUFA) decrease drastically in comparison to PC species with 2 or 1 double bonds during differentiation. In contrast, the content of ether-linked lipid species in both differentiated cell types increases. Consequently, lower PUFA content and higher ether lipid content should protect these blood cells optimally from ROS and age-related diseases after differentiation.

In contrast to the results above, (O'Rourke et al., 2013) found that supplementing C. elegans or human epithelial cells with PUFA increases their resistance to starvation and extends their life span in conditions of food abundance, via autophagy activation. Indeed, inactivation of autophagy reverses this effect (O'Rourke et al., 2013; Kniazeva and Han, 2013).

Surprisingly, in a review by (Puca et al., 2008), increased levels of endogenous trans fatty acids are associated with a predisposition to exceptional longevity. However, studies so far showed only that trans fatty acids decrease the rate of lipid peroxidation, an effect that may mitigate the atherogenic effect of these fatty acids (Sargis and Subbaiah, 2003).

Odd chain fatty acid metabolism might have an underestimated role in health and disease and longevity (Jenkins et al., 2015). Historically, odd chain saturated FAs (esterified in intact lipids) were used as internal standards in GC–MS (or LC–MS) methods, as it was thought that their concentrations were insignificant in humans. Later on, increased consumption of dairy products was associated with the increased blood plasma levels of odd chain FAs. However, there is evidence for an

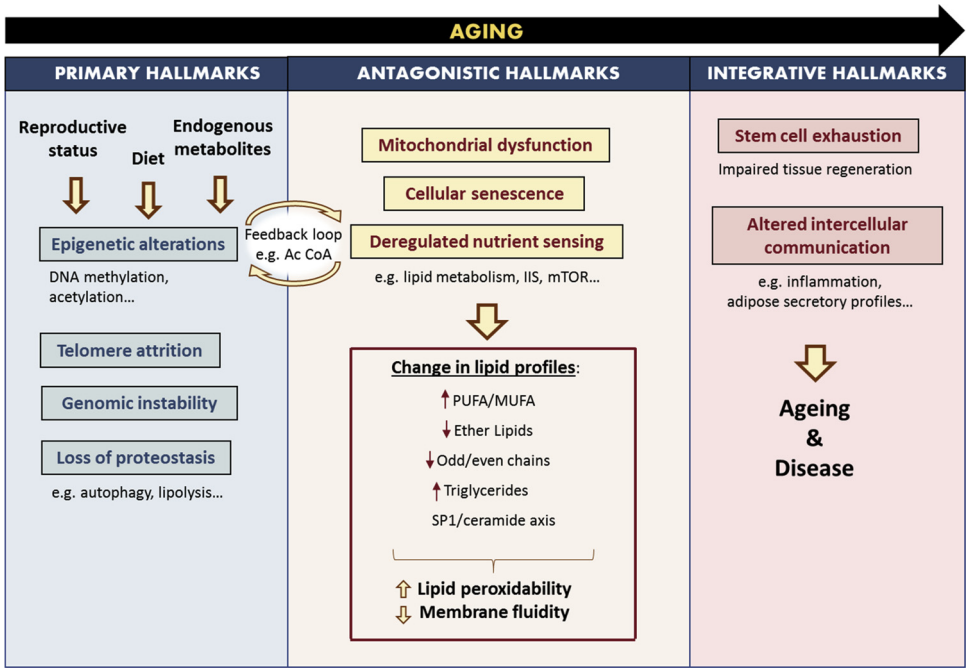

Fig. 4. Key aspects of lipids in aging and their connection to the hallmarks of aging.

endogenous metabolism of C 17:0 and C15:0. Furthermore, even and odd chain saturated FAs seem to have an inverse association with adipokine profiles, in glucose metabolism and type 2 diabetes (Kurotani et al., 2017).

While saturated FAs with even chains are associated with increased metabolic disease risk and aging, odd chain FAs (C:15, C:17) correlate with a reduced risk with C:17 having the strongest risk reduction. Furthermore circulating C:15 levels correlated with diary intake and C:17 seems to have other influencing factors (Jenkins et al., 2017). There is evidence that C:17 can be also biosynthesized in vivo in mammals (Wakil, 1966, 1965). However, odd numbered FAs are more likely to accumulate in the adipose tissue than even numbered FAs (Gotoh et al., 2008). In the review of Jenkins et al. (Jenkins et al., 2015) it is described that odd chain FAs increase membrane fluidity to a similar degree as PUFAs. Though, this hypothesis seems to be controversial, but is stemming from the fact that an odd-chain acid has a lower melting point than its next lower even-numbered homolog (Holman et al., 1995, 1989). Thus, FA C:15:0 has a lower melting point than FA C:14:0.

5.4. *Lipids as signaling molecules*

Steroids like molecules have an important function in longevity in different organism and many of their interactions have been identified. Mammalian nuclear hormone receptors (NHRs), such as liver X receptor, farnesoid X receptor, and peroxisome proliferator-activated receptors (PPARs), precisely control energy metabolism. Van Gilst et al. (Van Gilst et al., 2005) found that the two phenotypes of the nhr-49 knockout were linked to distinct pathways and were separable: The high-fat phenotype was due to reduced expression of enzymes in fatty acid β-oxidation, and the shortened adult life span resulted from impaired expression of stearoyl-CoA desaturase. Further studies by Pathare et al. (Pathare et al., 2012) suggest that NHR-80 and NHR-13′s modulation of NHR-49 regulated fatty acid desaturase genes contribute to the shortened lifespan phenotype of nhr-49 deletion mutant animals. Antebi (Antebi, 2013) reviewed how hormonal signaling is linked to the gonodal longevity pathway: Removal of the gonad or parts thereof can extent life span in a variety of species.

In C. elegans longevity was promoted by oleoylethanolamide (OEA), an N-acyl ethanolamine-derived lipid that was detected by high-throughput metabolomics analysis (Folick et al., 2015a). Because of the physiological importance of this molecule a novel GC–MS method has been recently developed to quantify this molecular specie accurately (Annibal et al., 2018).

6. Summary and conclusions

Lipids occur in a variety of sizes, biophysical properties, and relative abundance. Dietary lipids, de novo lipogenesis, and hundreds of enzymes influence together the lipid profile of an organism. Enzymes that are suggested to be involved in lipid metabolism of longevity modulate the length and desaturation of FA chains and their incorporation into more complex lipid molecules (Schroeder and Brunet, 2015). For instance, lipases liberate FAs from lipid molecules to serve as energy sources, as signaling molecule or for remodeling. Desaturases and elongases introduce new double bonds into FA chains and catalyze carbon chain extension, respectively. Thus, targeting such lipid signaling pathways with genetic, pharmacological or dietary interventions would probably affect longevity and help us understand better the role of lipid metabolism in the aging process.

One of the most studied interventions in these regards is caloric restriction, which successfully delays aging in a wide number of model organisms; however, despite all the literature on this topic, the underlying molecular and cellular mechanisms of CR are still not well understood. This might be due to its pleiotropic effects, as CR triggers a wide number of responses at different levels, affecting the epigenetic landscape and several metabolic pathways involved in maintenance and repair, nutrient sensing, cellular senescence and longevity. More research is needed regarding the CR effects on the metabolism of specific fatty acids, lipid profiles and epigenetic changes that may alter lipid signaling pathways.

In Fig. 4 the hallmarks of aging and their connection with lipid metabolism and profiles are schematically shown. One of the key aspects of lipids that affect the aging process has to do with their peroxidability: a higher MUFA/PUFA ratio clearly delays aging and age-related diseases in model organisms. Polyunsaturated lipids are particularly susceptible to the ROS attack, whereby saturated and monounsaturated fatty acyl chains (SFA and MUFA) are essentially resistant

to peroxidation that would act further as amplifiers of oxidative stress. Other obvious changes in long-lived animals are an increase of specific odd chain FAs and an increase in ether lipids. While odd chain FAs increase the fluidity similar to PUFAs, they are resistant to ROS like SFA. In addition, ether lipids are the pre-stage of vinyl-ether PLs (plasmalogens), which are discussed as efficient antioxidants.

In contrast to these findings, it is of great interest the fact that dietary intake of saturated FAs has been mistakenly regarded -and still remains to be- as a major culprit of obesity and cardiovascular diseases and is also associated with a higher risk of all-cause mortality. However, recent meta-analyses cannot find significant evidence of such associations (Siri-Tarino et al., 2010; de Souza et al., 2015; Harcombe et al., 2015) and more care should be placed when developing dietary guidelines. It would be of interest to determine the relative effects of different saturated FAs at different levels, such as peroxidability and atherogenic capacity, as well as developing more randomized controlled trials rather than observational and epidemiological studies.

Acknowledgements

This study was supported by the German Research Council (DFG FU 771/1-3).

References

A J, Trygg, J., Gullberg, J., Johansson, A.I., Jonsson, P., Antti, H., Marklund, S.L., Moritz, T., 2005. Extraction and GC/MS analysis of the human blood plasma metabolome. Anal. Chem. 77, 8086–8094.
Ahuja, G., Bartsch, D., Yao, W., Geissen, S., Frank, S., Aguirre, A., Russ, N., Messling, J.E., Dodzian, J., Lagerborg, K.A., Vargas, N.E., Muck, J.S., Brodesser, S., Baldus, S., Sachinidis, A., Hescheler, J., Dieterich, C., Trifunovic, A., Papantonis, A., Petrascheck, M., Klinke, A., Jain, M., Valenzano, D.R., Kurian, L., 2019. Loss of genomic integrity induced by lysosphingolipid imbalance drives ageing in the heart. EMBO Rep. 20.
Altintas, O., Park, S., Lee, S.J., 2016. The role of insulin/IGF-1 signaling in the longevity of model invertebrates, C. Elegans and D. Melanogaster. BMB Rep. 49, 81–92.
Amoscato, A.A., Sparvero, L.J., He, R.R., Watkins, S., Bayir, H., Kagan, V.E., 2014. Imaging mass spectrometry of diversified cardiolipin molecular species in the brain. Anal. Chem. 86, 6587–6595.
Anderson, R.M., Weindruch, R., 2010. Metabolic reprogramming, caloric restriction and aging. Trends Endocrinol. Metab. 21, 134–141.
Anisimov, V.N., 2013. Metformin: do we finally have an anti-aging drug? Cell Cycle 12, 3483–3489.
Annibal, A., Karalay, O., Latza, C., Antebi, A., 2018. A novel EI-GC/MS method for the accurate quantification of anti-aging compound oleoylethanolamine in C. Elegans. Anal. Methods 10, 2551–2559.
Antebi, A., 2013. Steroid regulation of C. Elegans diapause, developmental timing, and longevity. Curr. Top. Dev. Biol. 105, 181–212.
Aramburu, J., Ortells, M.C., Tejedor, S., Buxade, M., Lopez-Rodriguez, C., 2014. Transcriptional regulation of the stress response by mTOR. Sci. Signal. 7, re2.
Arantes-Oliveira, N., Apfeld, J., Dillin, A., Kenyon, C., 2002. Regulation of life-span by germ-line stem cells in Caenorhabditis elegans. Science 295, 502–505.
Arguelles, S., Camandola, S., Cutler, R.G., Ayala, A., Mattson, M.P., 2014. Elongation factor 2 diphthamide is critical for translation of two IRES-dependent protein targets, XIAP and FGF2, under oxidative stress conditions. Free Radic. Biol. Med. 67, 131–138.
Ayala, A., Munoz, M.F., Arguelles, S., 2014. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid. Med. Cell. Longev. 2014, 360438.
Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., Van Deursen, J.M., 2016. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature 530, 184–189.
Baker, D.J., Peleg, S., 2017. Biphasic modeling of mitochondrial metabolism dysregulation during aging. Trends Biochem. Sci. 42, 702–711.
Baker, D.J., Wijshake, T., Tchkonia, T., Lebrasseur, N.K., Childs, B.G., Van De Sluis, B., Kirkland, J.L., Van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236.
Balcombe, N.R., Sinclair, A., 2001. Ageing: definitions, mechanisms and the magnitude of the problem. Best Pract. Res. Clin. Gastroenterol. 15, 835–849.
Barnes, A.I., Boone, J.M., Jacobson, J., Partridge, L., Chapman, T., 2006. No extension of lifespan by ablation of germ line in Drosophila. Proc. Biol. Sci. 273, 939–947.
Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., De Cabo, R., Sinclair, D.A., 2006. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444, 337–342.
Berman, J.R., Kenyon, C., 2006. Germ-cell loss extends C. Elegans life span through regulation of DAF-16 by kri-1 and lipophilic-hormone signaling. Cell 124, 1055–1068.
Bettedi, L., Foukas, L.C., 2017. Growth factor, energy and nutrient sensing signalling pathways in metabolic ageing. Biogerontology 18, 913–929.
Blagosklonny, M.V., 2012. Rapalogs in cancer prevention: anti-aging or anticancer? Cancer Biol. Ther. 13, 1349–1354.
Blasco, M.A., 2007. Telomere length, stem cells and aging. Nat. Chem. Biol. 3, 640–649.
Bligh, E.G., Dyer, W.J., 1959. A rapid method of total lipid extraction and purification. Can. J. Biochem. Physiol. 37, 911–917.
Bonkowski, M.S., Sinclair, D.A., 2016. Slowing ageing by design: the rise of NAD(+) and sirtuin-activating compounds. Nat. Rev. Mol. Cell Biol. 17, 679–690.
Braidy, N., Guillemin, G.J., Mansour, H., Chan-Ling, T., Poljak, A., Grant, R., 2011. Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats. PLoS One 6, e19194.
Braverman, N.E., Moser, A.B., 2012. Functions of plasmalogen lipids in health and disease. Biochim. Biophys. Acta 1822, 1442–1452.
Brosche, T., Platt, D., 1998. The biological significance of plasmalogens in defense against oxidative damage. Exp. Gerontol. 33, 363–369.
Brugger, B., 2014. Lipidomics: analysis of the lipid composition of cells and subcellular organelles by electrospray ionization mass spectrometry. Annu. Rev. Biochem. 83 (83), 79–98.
Brunet, A., Rando, T.A., 2017. Interaction between epigenetic and metabolism in aging stem cells. Curr. Opin. Cell Biol. 45, 1–7.
Bruning, J.C., Gautam, D., Burks, D.J., Gillette, J., Schubert, M., Orban, P.C., Klein, R., Krone, W., Muller-Wieland, D., Kahn, C.R., 2000. Role of brain insulin receptor in control of body weight and reproduction. Science 289, 2122–2125.
Burkle, A., Caselli, G., Franceschi, C., Mariani, E., Sansoni, P., Santoni, A., Vecchio, G., Witkowski, J.M., Caruso, C., 2007. Pathophysiology of ageing, longevity and age related diseases. Immun. Ageing 4, 4.
Burks, D.J., Font De Mora, J., Schubert, M., Withers, D.J., Myers, M.G., Towery, H.H., Altamuro, S.L., Flint, C.L., White, M.F., 2000. IRS-2 pathways integrate female reproduction and energy homeostasis. Nature 407, 377–382.
Bustos, V., Partridge, L., 2017. Good Ol' fat: links between lipid signaling and longevity. Trends Biochem. Sci. 42, 812–823.
Cajka, T., Fiehn, O., 2016. Toward merging untargeted and targeted methods in mass spectrometry-based metabolomics and lipidomics. Anal. Chem. 88, 524–545.
Canto, C., Auwerx, J., 2012. Targeting sirtuin 1 to improve metabolism: all you need is NAD(+)? Pharmacol. Rev. 64, 166–187.
Caron, A., Richard, D., Laplante, M., 2015. The roles of mTOR complexes in lipid metabolism. Annu. Rev. Nutr. 35, 321–348.
Chicco, A.J., Sparagna, G.C., 2007. Role of cardiolipin alterations in mitochondrial dysfunction and disease. Am. J. Physiol., Cell Physiol. 292, C33–44.
Clancy, D.J., Gems, D., Hafen, E., Leevers, S.J., Partridge, L., 2002. Dietary restriction in long-lived dwarf flies. Science 296, 319.
Conboy, I.M., Rando, T.A., 2012. Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. Cell Cycle 11, 2260–2267.
Coppe, J.P., Desprez, P.Y., Krtolica, A., Campisi, J., 2010. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu. Rev. Pathol. 5, 99–118.
De Magalhaes, J.P., Church, G.M., 2005. Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology Bethesda (Bethesda) 20, 252–259.
De Souza, R.J., Mente, A., Maroleanu, A., Cozma, A.I., Ha, V., Kishibe, T., Uleryk, E., Budylowski, P., Schunemann, H., Beyene, J., Anand, S.S., 2015. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 351, h3978.
Dean, J.M., Lodhi, I.J., 2018. Structural and functional roles of ether lipids. Protein Cell 9, 196–206.
Di Francesco, A., Di Germanio, C., Bernier, M., De Cabo, R., 2018. A time to fast. Science 362, 770–775.
Ditz, T., Schnapka-Hille, L., Noack, N., Dorow, J., Ceglarek, U., Niederwieser, D., Schiller, J., Fuchs, B., Cross, M., 2018. Phospholipase A2 products predict the hematopoietic support capacity of horse serum. Differentiation 105, 27–32.
Droge, W., 2002. The plasma redox state and ageing. Ageing Res. Rev. 1, 257–278.
Ellis, S.R., Brown, S.H., In Het Panhuis, M., Blanksby, S.J., Mitchell, T.W., 2013. Surface analysis of lipids by mass spectrometry: more than just imaging. Prog. Lipid Res. 52, 329–353.
Erickson, N.E., Lands, W.E., 1959. Plasmalogen in the developing brain. Proc. Soc. Exp. Biol. Med. 102, 512–514.
Farooqui, A.A., Horrocks, L.A., 2001. Plasmalogens: workhorse lipids of membranes in normal and injured neurons and glia. Neuroscientist 7, 232–245.
Farwanah, H., Kolter, T., Sandhoff, K., 2011. Mass spectrometric analysis of neutral sphingolipids: methods, applications, and limitations. Biochim. Biophys. Acta 1811, 854–860.
Flatt, T., Min, K.J., D'alterio, C., Villa-Cuesta, E., Cumbers, J., Lehmann, R., Jones, D.L., Tatar, M., 2008. Drosophila germ-line modulation of insulin signaling and lifespan. Proc Natl Acad Sci U S A 105, 6368–6373.
Folch, J., Lees, M., Sloane Stanley, G.H., 1957. A simple method for the isolation and purification of total lipides from animal tissues. J. Biol. Chem. 226, 497–509.
Folick, A., Oakley, H.D., Yu, Y., Armstrong, E.H., Kumari, M., Sanor, L., Moore, D.D., Ortlund, E.A., Zechner, R., Wang, M.C., 2015a. Aging. Lysosomal signaling molecules regulate longevity in Caenorhabditis elegans. Science 347, 83–86.
Folick, A., Oakley, H.D., Yu, Y., Armstrong, E.H., Kumari, M., Sanor, L., Moore, D.D., Ortlund, E.A., Zechner, R., Wang, M.C., 2015b. Lysosomal signaling molecules

regulate longevity in Caenorhabditis elegans. Science 347, 83–86.
Fontana, L., Meyer, T.E., Klein, S., Holloszy, J.O., 2004. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A 101, 6659–6663.
Fontana, L., Partridge, L., 2015. Promoting health and longevity through diet: from model organisms to humans. Cell 161, 106–118.
Fontana, L., Partridge, L., Longo, V.D., 2010. Extending healthy life span–from yeast to humans. Science 328, 321–326.
Fuchs, B., 2012. Analysis of phospolipids and glycolipids by thin-layer chromatography-matrix-assisted laser desorption and ionization mass spectrometry. J. Chromatogr. A 1259, 62–73.
Fuchs, B., 2015. Analytical methods for (oxidized) plasmalogens: methodological aspects and applications. Free Radic. Res. 49, 599–617.
Fuchs, B., Popkova, Y., Suss, R., Schiller, J., 2015. Separation of (Phospho)Lipids by Thin-Layer Chromatography. Instrumental Thin-Layer Chromatography, pp. 375–405.
Fuchs, B., Schnapka-Hille, L., Schiller, J., Cross, M.A., 2011a. Oxygen and cytokine-dependent changes in choline phospholipid saturation in hematopoietic progenitor cells detected by MALDI-TOF mass spectrometry. Chem. Phys. Lipids 164, 636–642.
Fuchs, B., Suss, R., Teuber, K., Eibisch, M., Schiller, J., 2011b. Lipid analysis by thin-layer chromatography–a review of the current state. J. Chromatogr. A 1218, 2754–2774.
Fulop, T., Le Page, A., Garneau, H., Azimi, N., Baehl, S., Dupuis, G., Pawelec, G., Larbi, A., 2012. Aging, immunosenescence and membrane rafts: the lipid connection. Longev. Healthspan 1, 6.
Garratt, M., Nakagawa, S., Simons, M.J., 2016. Comparative idiosyncrasies in life extension by reduced mTOR signalling and its distinctiveness from dietary restriction. Aging Cell 15, 737–743.
Gertz, M., Nguyen, G.T., Fischer, F., Suenkel, B., Schlicker, C., Franzel, B., Tomaschewski, J., Aladini, F., Becker, C., Wolters, D., Steegborn, C., 2012. A molecular mechanism for direct sirtuin activation by resveratrol. PLoS One 7, e49761.
Ghazi, A., 2013. Transcriptional networks that mediate signals from reproductive tissues to influence lifespan. Genesis 51, 1–15.
Gonzalez-Covarrubias, V., 2013. Lipidomics in longevity and healthy aging. Biogerontology 14, 663–672.
Gotoh, N., Moroda, K., Watanabe, H., Yoshinaga, K., Tanaka, M., Mizobe, H., Ichioka, K., Tokairin, S., Wada, S., 2008. Metabolism of odd-numbered fatty acids and even-numbered fatty acids in mouse. J. Oleo Sci. 57, 293–299.
Green, C., Mitchell, S., Speakman, J., 2017. Energy balance and the sphingosine-1-phosphate/ceramide axis. Aging (Albany NY) 9, 2463–2464.
Greer, E.L., Brunet, A., 2009. Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in C. Elegans. Aging Cell 8, 113–127.
Gross, R.W., 2017. The evolution of lipidomics through space and time. Biochim. Biophys Acta. Mol. Cell Biol. Lipids. 1862, 731–739.
Guarente, L., 2013. Calorie restriction and sirtuins revisited. Genes Dev. 27, 2072–2085.
Gut, P., Verdin, E., 2013. The nexus of chromatin regulation and intermediary metabolism. Nature 502, 489–498.
Hahn, O., Gronke, S., Stubbs, T.M., Ficz, G., Hendrich, O., Krueger, F., Andrews, S., Zhang, Q., Wakelam, M.J., Beyer, A., Reik, W., Partridge, L., 2017. Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. Genome Biol. 18, 56.
Halade, G.V., Kain, V., Black, L.M., Prabhu, S.D., Ingle, K.A., 2016. Aging dysregulates D- and E-series resolvins to modulate cardiosplenic and cardiorenal network following myocardial infarction. Aging (Albany NY) 8, 2611–2634.
Han, S., Schroeder, E.A., Silva-Garcia, C.G., Hebestreit, K., Mair, W.B., Brunet, A., 2017. Mono-unsaturated fatty acids link H3K4me3 modifiers to C. Elegans lifespan. Nature 544, 185–190.
Han, X.L., Gross, R.W., 2005. Shotgun lipidomics: electrospray ionization mass spectrometric analysis and quantitation of cellular lipidomes directly from crude extracts of biological samples. Mass Spectrom. Rev. 24, 367–412.
Han, X.L., Yang, K., Cheng, H., Fikes, K.N., Gross, R.W., 2005. Shotgun lipidomics of phosphoethanolamine-containing lipids in biological samples after one-step in situ derivatization. J. Lipid Res. 46, 1548–1560.
Han, X.L., Yang, K., Yang, J.Y., Cheng, H., Gross, R.W., 2006. Shotgun lipidomics of cardiolipin molecular species in lipid extracts of biological samples. J. Lipid Res. 47, 864–879.
Hancock, C.R., Han, D.H., Higashida, K., Kim, S.H., Holloszy, J.O., 2011. Does calorie restriction induce mitochondrial biogenesis? A reevaluation. FASEB J. 25, 785–791.
Hansen, M., Flatt, T., Aguilaniu, H., 2013. Reproduction, fat metabolism, and life span: what is the connection? Cell Metab. 17, 10–19.
Harcombe, Z., Baker, J.S., Cooper, S.M., Davies, B., Sculthorpe, N., Dinicolantonio, J.J., Grace, F., 2015. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2, e000196.
Harrison, D.E., Strong, R., Sharp, Z.D., Nelson, J.F., Astle, C.M., Flurkey, K., Nadon, N.L., Wilkinson, J.E., Frenkel, K., Carter, C.S., Pahor, M., Javors, M.A., Fernandez, E., Miller, R.A., 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460, 392–395.
Hekimi, S., Lapointe, J., Wen, Y., 2011. Taking a "good" look at free radicals in the aging process. Trends Cell Biol. 21, 569–576.
Holman, R.T., Adams, C.E., Nelson, R.A., Grater, S.J., Jaskiewicz, J.A., Johnson, S.B., Erdman Jr, J.W., 1995. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. J. Nutr. 125, 901–907.
Holman, R.T., Johnson, S.B., Kokmen, E., 1989. Deficiencies of polyunsaturated fatty acids and replacement by nonessential fatty acids in plasma lipids in multiple sclerosis. Proc. Natl. Acad. Sci. U S A 86, 4720–4724.
Houtkooper, R.H., Pirinen, E., Auwerx, J., 2012. Sirtuins as regulators of metabolism and healthspan. Nat. Rev. Mol. Cell Biol. 13, 225–238.
Hsin, H., Kenyon, C., 1999. Signals from the reproductive system regulate the lifespan of C. Elegans. Nature 399, 362–366.
Hulbert, A.J., 2003. Life, death and membrane bilayers. J. Exp. Biol. 206, 2303–2311.
Hulbert, A.J., 2005. On the importance of fatty acid composition of membranes for aging. J. Theor. Biol. 234, 277–288.
Hulbert, A.J., Pamplona, R., Buffenstein, R., Buttemer, W.A., 2007. Life and death: metabolic rate, membrane composition, and life span of animals. Physiol. Rev. 87, 1175–1213.
Imhof, A., Peleg, S., 2016. From HDACi to KDACi: we need to revisit non-epigenetic pathways affected by inhibiting lysine deacetylases in therapy. EMBO Rep. 17, 1673.
Jenkins, B., West, J.A., Koulman, A., 2015. A review of odd-chain fatty acid metabolism and the role of pentadecanoic Acid (c15:0) and heptadecanoic Acid (c17:0) in health and disease. Molecules 20, 2425–2444.
Jenkins, B.J., Seyssel, K., Chiu, S., Pan, P.-H., Lin, S.-Y., Stanley, E., Ament, Z., West, J.A., Summerhill, K., Griffin, J.L., Vetter, W., Autio, K.J., Hiltunen, K., Hazebrouck, S., Stepankova, R., Chen, C.-J., Alligier, M., Laville, M., Moore, M., Kraft, G., Cherrington, A., King, S., Krauss, R.M., De Schryver, E., Van Veldhoven, P.P., Ronis, M., Koulman, A., 2017. Odd Chain Fatty Acids; New Insights of the Relationship Between the Gut Microbiota, Dietary Intake, Biosynthesis and Glucose Intolerance. Sci. Rep. 7, 44845.
Johnson, S.C., Rabinovitch, P.S., Kaeberlein, M., 2013. mTOR is a key modulator of ageing and age-related disease. Nature 493, 338–345.
Jurowski, K., Kochan, K., Walczak, J., Baranska, M., Piekoszewski, W., Buszewski, B., 2017. Analytical techniques in Lipidomics: state of the art. Crit. Rev. Anal. Chem. 47, 418–437.
Kawanishi, N., Kato, Y., Yokozeki, K., Sawada, S., Sakurai, R., Fujiwara, Y., Shinkai, S., Goda, N., Suzuki, K., 2018. Effects of aging on serum levels of lipid molecular species as determined by lipidomics analysis in Japanese men and women. Lipids Health Dis. 17.
Kenyon, C., 2011. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 366, 9–16.
Kermorvant-Duchemin, E., Sennlaub, F., Sirinyan, M., Brault, S., Andelfinger, G., Kooli, A., Germain, S., Ong, H., D'orleans-Juste, P., Gobeil Jr, F., Zhu, T., Boisvert, C., Hardy, P., Jain, K., Falck, J.R., Balazy, M., Chemtob, S., 2005. Trans-arachidonic acids generated during nitrative stress induce a thrombospondin-1-dependent microvascular degeneration. Nat. Med. 11, 1339–1345.
Kniazeva, M., Han, M., 2013. Fat chance for longevity. Genes Dev. 27, 351–354.
Kohler, I., Verhoeven, A., Derks, R.J., Giera, M., 2016. Analytical pitfalls and challenges in clinical metabolomics. Bioanalysis 8, 1509–1532.
Kunkel, G.T., Maceyka, M., Milstien, S., Spiegel, S., 2013. Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. Nat. Rev. Drug Discov. 12, 688–702.
Kurotani, K., Sato, M., Yasuda, K., Kashima, K., Tanaka, S., Hayashi, T., Shirouchi, B., Akter, S., Kashino, I., Hayabuchi, H., Mizoue, T., 2017. Even- and odd-chain saturated fatty acids in serum phospholipids are differentially associated with adipokines. PLoS One 12, e0178192.
Laaksonen, R., Katajamaa, M., Paiva, H., Sysi-Aho, M., Saarinen, L., Junni, P., Lutjohann, D., Smet, J., Van Coster, R., Seppanen-Laakso, T., Lehtimaki, T., Soini, J., Oresic, M., 2006. A systems biology strategy reveals biological pathways and plasma biomarker candidates for potentially toxic statin-induced changes in muscle. PLoS One 1.
Labbadia, J., Morimoto, R.I., 2015. The biology of proteostasis in aging and disease. Annu. Rev. Biochem. 84, 435–464.
Laganiere, S., Yu, B.P., 1993. Modulation of membrane phospholipid fatty acid composition by age and food restriction. Gerontology 39, 7–18.
Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., Geny, B., Laakso, M., Puigserver, P., Auwerx, J., 2006. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 127, 1109–1122.
Lamming, D.W., Sabatini, D.M., 2013. A Central role for mTOR in lipid homeostasis. Cell Metab. 18, 465–469.
Lee, C., Longo, V., 2016. Dietary restriction with and without caloric restriction for healthy aging. F1000Res 5.
Lessig, J., Fuchs, B., 2009. Plasmalogens in biological systems: their role in oxidative processes in biological membranes, their contribution to pathological processes and aging and plasmalogen analysis. Curr. Med. Chem. 16, 2021–2041.
Li, M., Yang, L., Bai, Y., Liu, H.W., 2014. Analytical methods in Lipidomics and their applications. Anal. Chem. 86, 161–175.
Lipsky, M.S., King, M., 2015. Biological theories of aging. Dis. 61, 460–466.
Longatti, A., Lamb, C.A., Razi, M., Yoshimura, S., Barr, F.A., Tooze, S.A., 2012. TBC1D14 regulates autophagosome formation via Rab11- and ULK1-positive recycling endosomes. J. Cell Biol. 197, 659–675.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Lopez-Otin, C., Galluzzi, L., Freije, J.M.P., Madeo, F., Kroemer, G., 2016. Metabolic control of longevity. Cell 166, 802–821.
Lu, C., Thompson, C.B., 2012. Metabolic regulation of epigenetics. Cell Metab. 16, 9–17.
Lu, S.P., Lin, S.J., 2010. Regulation of yeast sirtuins by NAD(+) metabolism and calorie restriction. Biochim. Biophys. Acta 1804, 1567–1575.
Luberto, C., Haley, J.D., Del Poeta, M., 2019. Imaging with mass spectrometry, the next frontier in sphingolipid research? A discussion on where we stand and the possibilities ahead. Chem. Phys. Lipids 219, 1–14.
Maeba, R., Maeda, T., Kinoshita, M., Takao, K., Takenaka, H., Kusano, J., Yoshimura, N., Takeoka, Y., Yasuda, D., Okazaki, T., Teramoto, T., 2007. Plasmalogens in human serum positively correlate with high- density lipoprotein and decrease with aging. J.

Atheroscler. Thromb. 14, 12–18.
Maegawa, S., Lu, Y., Tahara, T., Lee, J.T., Madzo, J., Liang, S., Jelinek, J., Colman, R.J., Issa, J.J., 2017. Caloric restriction delays age-related methylation drift. Nat. Commun. 8, 539.
Maftah, A., Ratinaud, M.H., Dumas, M., Bonte, F., Meybeck, A., Julien, R., 1994. Human epidermal cells progressively lose their cardiolipins during ageing without change in mitochondrial transmembrane potential. Mech. Ageing Dev. 77, 83–96.
Maklakov, A.A., Immler, S., 2016. The expensive germline and the evolution of ageing. Curr. Biol. 26, R577–R586.
Martin, B., Golden, E., Carlson, O.D., Egan, J.M., Mattson, M.P., Maudsley, S., 2008. Caloric restriction: impact upon pituitary function and reproduction. Ageing Res. Rev. 7, 209–224.
Martins, R., Lithgow, G.J., Link, W., 2016. Long live FOXO: unraveling the role of FOXO proteins in aging and longevity. Aging Cell 15, 196–207.
Masoro, E.J., 2005. Overview of caloric restriction and ageing. Mech. Ageing Dev. 126, 913–922.
Massudi, H., Grant, R., Braidy, N., Guest, J., Farnsworth, B., Guillemin, G.J., 2012. Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. PLoS One 7, e42357.
Matjusaitis, M., Chin, G., Sarnoski, E.A., Stolzing, A., 2016. Biomarkers to identify and isolate senescent cells. Ageing Res. Rev. 29, 1–12.
Mattison, J.A., Colman, R.J., Beasley, T.M., Allison, D.B., Kemnitz, J.W., Roth, G.S., Ingram, D.K., Weindruch, R., De Cabo, R., Anderson, R.M., 2017. Caloric restriction improves health and survival of rhesus monkeys. Nat. Commun. 8, 14063.
Mattson, M.P., Allison, D.B., Fontana, L., Harvie, M., Longo, V.D., Malaisse, W.J., Mosley, M., Notterpek, L., Ravussin, E., Scheer, F.A., Seyfried, T.N., Varady, K.A., Panda, S., 2014. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 111, 16647–16653.
Maulucci, G., Daniel, B., Cohen, O., Avrahami, Y., Sasson, S., 2016. Hormetic and regulatory effects of lipid peroxidation mediators in pancreatic beta cells. Mol. Aspects Med. 49, 49–77.
Medvedev, Z.A., 1990. An attempt at a rational classification of theories of ageing. Biol. Rev. Camb. Philos. Soc. 65, 375–398.
Miller, K.N., Burhans, M.S., Clark, J.P., Howell, P.R., Polewski, M.A., Demuth, T.M., Eliceiri, K.W., Lindstrom, M.J., Ntambi, J.M., Anderson, R.M., 2017. Aging and caloric restriction impact adipose tissue, adiponectin, and circulating lipids. Aging Cell 16, 497–507.
Minor, R.K., Baur, J.A., Gomes, A.P., Ward, T.M., Csiszar, A., Mercken, E.M., Abdelmohsen, K., Shin, Y.K., Canto, C., Scheibye-Knudsen, M., Krawczyk, M., Irusta, P.M., Martin-Montalvo, A., Hubbard, B.P., Zhang, Y., Lehrmann, E., White, A.A., Price, N.L., Swindell, W.R., Pearson, K.J., Becker, K.G., Bohr, V.A., Gorospe, M., Egan, J.M., Talan, M.I., Auwerx, J., Westphal, C.H., Ellis, J.L., Ungvari, Z., Vlasuk, G.P., Elliott, P.J., Sinclair, D.A., De Cabo, R., 2011. SRT1720 improves survival and healthspan of obese mice. Sci. Rep. 1, 70.
Mirzaei, H., Suarez, J.A., Longo, V.D., 2014. Protein and amino acid restriction, aging and disease: from yeast to humans. Trends Endocrinol. Metab. 25, 558–566.
Moskalev, A.A., Shaposhnikov, M.V., Plyusnina, E.N., Zhavoronkov, A., Budovsky, A., Yanai, H., Fraifeld, V.E., 2013. The role of DNA damage and repair in aging through the prism of Koch-like criteria. Ageing Res. Rev. 12, 661–684.
Most, J., Tosti, V., Redman, L.M., Fontana, L., 2017. Calorie restriction in humans: an update. Ageing Res. Rev. 39, 36–45.
Mouchiroud, L., Houtkooper, R.H., Moullan, N., Katsyuba, E., Ryu, D., Canto, C., Mottis, A., Jo, Y.S., Viswanathan, M., Schoonjans, K., Guarente, L., Auwerx, J., 2013. The NAD(+)/Sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell 154, 430–441.
Muller, F.L., Lustgarten, M.S., Jang, Y., Richardson, A., Van Remmen, H., 2007. Trends in oxidative aging theories. Free Radic. Biol. Med. 43, 477–503.
Munro, D., Blier, P.U., 2012. The extreme longevity of Arctica islandica is associated with increased peroxidation resistance in mitochondrial membranes. Aging Cell 11, 845–855.
Murphy, C.T., Mccarroll, S.A., Bargmann, C.I., Fraser, A., Kamath, R.S., Ahringer, J., Li, H., Kenyon, C., 2003. Genes that act downstream of DAF-16 to influence the lifespan of Caenorhabditis elegans. Nature 424, 277–283.
Nakamura, Y., Shimizu, Y., Horibata, Y., Tei, R., Koike, R., Masawa, M., Watanabe, T., Shiobara, T., Arai, R., Chibana, K., Takemasa, A., Sugimoto, H., Ishii, Y., 2017. Changes of plasmalogen phospholipid levels during differentiation of induced pluripotent stem cells 409B2 to endothelial phenotype cells. Sci. Rep. 7, 9377.
Naude, C.E., Visser, M.E., Nguyen, K.A., Durao, S., Schoonees, A., 2018. Effects of total fat intake on bodyweight in children. Cochrane Database Syst. Rev. 7, CD012960.
Naudi, A., Cabre, R., Jove, M., Ayala, V., Gonzalo, H., Portero-Otin, M., Ferrer, I., Pamplona, R., 2015. Lipidomics of human brain aging and Alzheimer's disease pathology. Int. Rev. Neurobiol. 122, 133–189.
Nelson, J.F., Strong, R., Bokov, A., Diaz, V., Ward, W., 2012. Probing the relationship between insulin sensitivity and longevity using genetically modified mice. J. Gerontol. A Biol. Sci. Med. Sci. 67, 1332–1338.
Newman, J.C., Covarrubias, A.J., Zhao, M., Yu, X., Gut, P., Ng, C.P., Huang, Y., Haldar, S., Verdin, E., 2017. Ketogenic diet reduces midlife mortality and improves memory in aging mice. Cell Metab. 26, 547–557 e8.
Nisoli, E., Tonello, C., Cardile, A., Cozzi, V., Bracale, R., Tedesco, L., Falcone, S., Valerio, A., Cantoni, O., Clementi, E., Moncada, S., Carruba, M.O., 2005. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science 310, 314–317.
O'rourke, E.J., Kuballa, P., Xavier, R., Ruvkun, G., 2013. omega-6 Polyunsaturated fatty acids extend life span through the activation of autophagy. Genes Dev. 27, 429–440.
Pamplona, R., Portero-Otin, M., Riba, D., Requena, J.R., Thorpe, S.R., Lopez-Torres, M., Barja, G., 2000a. Low fatty acid unsaturation: a mechanism for lowered lipoperoxidative modification of tissue proteins in mammalian species with long life spans. J. Gerontol. A Biol. Sci. Med. Sci. 55, B286–B291.
Pamplona, R., Portero-Otin, M., Ruiz, C., Gredilla, R., Herrero, A., Barja, G., 2000b. Double bond content of phospholipids and lipid peroxidation negatively correlate with maximum longevity in the heart of mammals. Mech. Ageing Dev. 112, 169–183.
Papsdorf, K., Brunet, A., 2019. Linking lipid metabolism to chromatin regulation in aging. Trends Cell Biol. 29 (2), 97–116.
Partridge, L., Gems, D., Withers, D.J., 2005. Sex and death: what is the connection? Cell 120, 461–472.
Pathare, P.P., Lin, A., Bornfeldt, K.E., Taubert, S., Van Gilst, M.R., 2012. Coordinate regulation of lipid metabolism by novel nuclear receptor partnerships. PLoS Genet. 8, e1002645.
Patti, G.J., Yanes, O., Siuzdak, G., 2012. Metabolomics: the apogee of the omics trilogy. Nat. Rev. Mol. Cell Biol. 13, 263–269.
Peleg, S., Feller, C., Forne, I., Schiller, E., Sevin, D.C., Schauer, T., Regnard, C., Straub, T., Prestel, M., Klima, C., Schmitt Nogueira, M., Becker, L., Klopstock, T., Sauer, U., Becker, P.B., Imhof, A., Ladurner, A.G., 2016a. Life span extension by targeting a link between metabolism and histone acetylation in Drosophila. EMBO Rep. 17, 455–469.
Peleg, S., Feller, C., Ladurner, A.G., Imhof, A., 2016b. The metabolic impact on histone acetylation and transcription in ageing. Trends Biochem. Sci. 41, 700–711.
Pellegrino, R.M., Di Veroli, A., Valeri, A., Goracci, L., Cruciani, G., 2014. LC/MS lipid profiling from human serum: a new method for global lipid extraction. Anal. Bioanal. Chem. 406, 7937–7948.
Portero-Otin, M., Bellmunt, M.J., Ruiz, M.C., Barja, G., Pamplona, R., 2001. Correlation of fatty acid unsaturation of the major liver mitochondrial phospholipid classes in mammals to their maximum life span potential. Lipids 36, 491–498.
Puca, A.A., Chatgilialoglu, C., Ferreri, C., 2008. Lipid metabolism and diet: possible mechanisms of slow aging. Int. J. Biochem. Cell Biol. 40, 324–333.
Quiros, P.M., Mottis, A., Auwerx, J., 2016. Mitonuclear communication in homeostasis and stress. Nat. Rev. Mol. Cell Biol. 17, 213–226.
Rattan, S.I., 2008. Hormesis in aging. Ageing Res. Rev. 7, 63–78.
Riera, C.E., Dillin, A., 2015. Tipping the metabolic scales towards increased longevity in mammals. Nat. Cell Biol. 17, 196–203.
Ristow, M., Schmeisser, K., 2014. Mitohormesis: promoting health and lifespan by increased levels of reactive oxygen species (ROS). Dose. 12, 288–341.
Roberts, M.N., Wallace, M.A., Tomilov, A.A., Zhou, Z., Marcotte, G.R., Tran, D., Perez, G., Gutierrez-Casado, E., Koike, S., Knotts, T.A., Imai, D.M., Griffey, S.M., Kim, K., Hagopian, K., Mcmackin, M.Z., Haj, F.G., Baar, K., Cortopassi, G.A., Ramsey, J.J., Lopez-Dominguez, J.A., 2017. A ketogenic diet extends longevity and healthspan in adult mice. Cell Metab. 26, 539–546 e5.
Rouser, G., Yamamoto, A., 1968. Curvilinear regression course of human brain lipid composition changes with age. Lipids 3, 284–287.
Sargis, R.M., Subbaiah, P.V., 2003. Trans unsaturated fatty acids are less oxidizable than cis unsaturated fatty acids and protect endogenous lipids from oxidation in lipoproteins and lipid bilayers. Biochemistry 42, 11533–11543.
Schieber, M., Chandel, N.S., 2014. ROS function in redox signaling and oxidative stress. Curr. Biol. 24, R453–62.
Schroeder, E.A., Brunet, A., 2015. Lipid profiles and signals for long life. Trends Endocrinol. Metab. 26, 589–592.
Schumacher, B., Van Der Pluijm, I., Moorhouse, M.J., Kosteas, T., Robinson, A.R., Suh, Y., Breit, T.M., Van Steeg, H., Niedernhofer, L.J., Van Ijcken, W., Bartke, A., Spindler, S.R., Hoeijmakers, J.H., Van Der Horst, G.T., Garinis, G.A., 2008. Delayed and accelerated aging share common longevity assurance mechanisms. PLoS Genet. 4, e1000161.
Schwudke, D., Oegema, J., Burton, L., Entchev, E., Hannich, J.T., Ejsing, C.S., Kurzchalia, T., Shevchenko, A., 2006. Lipid profiling by multiple precursor and neutral loss scanning driven by the data-dependent acquisition. Anal. Chem. 78, 585–595.
Selman, C., Partridge, L., Withers, D.J., 2011. Replication of extended lifespan phenotype in mice with deletion of insulin receptor substrate 1. PLoS One 6, e16144.
Seppanen-Laakso, T., Oresic, M., 2009. How to study lipidomes. J. Mol. Endocrinol. 42, 185–190.
Shaw, A.C., Joshi, S., Greenwood, H., Panda, A., Lord, J.M., 2010. Aging of the innate immune system. Curr. Opin. Immunol. 22, 507–513.
Shimokawa, I., Trindade, L.S., 2010. Dietary restriction and aging in rodents: a current view on its molecular mechanisms. Aging Dis. 1, 89–107.
Shmookler Reis, R.J., Xu, L., Lee, H., Chae, M., Thaden, J.J., Bharill, P., Tazearslan, C., Siegel, E., Alla, R., Zimniak, P., Ayyadevara, S., 2011. Modulation of lipid biosynthesis contributes to stress resistance and longevity of C. Elegans mutants. Aging (Albany NY) 3, 125–147.
Siri-Tarino, P.W., Sun, Q., Hu, F.B., Krauss, R.M., 2010. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am. J. Clin. Nutr. 91, 535–546.
Soliman, G.A., 2011. The integral role of mTOR in lipid metabolism. Cell Cycle 10, 861–862.
Sommer, U., Herscovitz, H., Welty, F.K., Costello, C.E., 2006. LC-MS-based method for the qualitative and quantitative analysis of complex lipid mixtures. J. Lipid Res. 47, 804–814.
Spiegel, S., Milstien, S., 2011. The outs and the ins of sphingosine-1-phosphate in immunity. Nat. Rev. Immunol. 11, 403–415.
Stepanova, M., Rodriguez, E., Birerdinc, A., Baranova, A., 2015. Age-independent rise of inflammatory scores may contribute to accelerated aging in multi-morbidity. Oncotarget 6, 1414–1421.
Templeman, N.M., Flibotte, S., Chik, J.H.L., Sinha, S., Lim, G.E., Foster, L.J., Nislow, C., Johnson, J.D., 2017. Reduced circulating insulin enhances insulin sensitivity in old mice and extends lifespan. Cell Rep. 20, 451–463.
Tumanov, S., Kamphorst, J.J., 2017. Recent advances in expanding the coverage of the

lipidome. Curr. Opin. Biotechnol. 43, 127–133.
Tyurina, Y.Y., Domingues, R.M., Tyurin, V.A., Maciel, E., Domingues, P., Amoscato, A.A., Bayir, H., Kagan, V.E., 2014. Characterization of cardiolipins and their oxidation products by LC-MS analysis. Chem. Phys. Lipids 179, 3–10.
Uhlenhaut, N.H., Treier, M., 2011. Forkhead transcription factors in ovarian function. Reproduction 142, 489–495.
Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T., Mazur, M., Telser, J., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39, 44–84.
Van Gilst, M.R., Hadjivassiliou, H., Jolly, A., Yamamoto, K.R., 2005. Nuclear hormone receptor NHR-49 controls fat consumption and fatty acid composition in C. Elegans. PLoS Biol. 3, e53.
Velarde, M.C., Demaria, M., Campisi, J., 2013. Senescent cells and their secretory phenotype as targets for cancer therapy. Interdiscip. Top. Gerontol. 38, 17–27.
Velazquez, A.P., Tatsuta, T., Ghillebert, R., Drescher, I., Graef, M., 2016. Lipid droplet-mediated ER homeostasis regulates autophagy and cell survival during starvation. J. Cell Biol. 212, 621–631.
Wakil, S.J., 1965. Mechanism of fatty-acid biosynthesis. Science 150 388-&.
Wakil, S.J., 1966. Biosynthesis of unsaturated fatty acids. J. Am. Oil Chem. Soc. 43 A135-&.
Wang, M., Wang, C., Han, R.H., Han, X., 2016. Novel advances in shotgun lipidomics for biology and medicine. Prog. Lipid Res. 61, 83–108.
Want, E.J., Cravatt, B.F., Siuzdak, G., 2005. The expanding role of mass spectrometry in metabolite profiling and characterization. Chembiochem 6, 1941–1951.
Watson, A.D., 2006. Lipidomics: a global approach to lipid analysis in biological systems. J. Lipid Res. 47, 2101–2111.
Wei, Y.H., Wu, S.B., Ma, Y.S., Lee, H.C., 2009. Respiratory function decline and DNA mutation in mitochondria, oxidative stress and altered gene expression during aging. Chang Gung Med. J. 32, 113–132.
Weindruch, R., Walford, R.L., Fligiel, S., Guthrie, D., 1986. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. J. Nutr. 116, 641–654.
Weisser, M., Spiteller, G., 1996. Increase of aldehydic compounds derived from plasmalogens in the brain of aged cattle. Chem. Phys. Lipids 82, 173–178.
Weisser, M., Vieth, M., Stolte, M., Riederer, P., Pfeuffer, R., Leblhuber, F., Spiteller, G., 1997. Dramatic increase of alpha-hydroxyaldehydes derived from plasmalogens in the aged human brain. Chem. Phys. Lipids 90, 135–142.
Yamazaki, Y., Kondo, K., Maeba, R., Nishimukai, M., Nezu, T., Hara, H., 2014. Proportion of nervonic acid in serum lipids is associated with serum plasmalogen levels and metabolic syndrome. J. Oleo Sci. 63, 527–537.
Yang, K., Han, X., 2016. Lipidomics: techniques, applications, and outcomes related to biomedical sciences. Trends Biochem. Sci. 41, 954–969.
Yetukuri, L., Ekroos, K., Vidal-Puig, A., Oresic, M., 2008. Informatics and computational strategies for the study of lipids. Mol. Biosyst. 4, 121–127.
Yu, B.P., Suescun, E.A., Yang, S.Y., 1992. Effect of age-related lipid peroxidation on membrane fluidity and phospholipase A2: modulation by dietary restriction. Mech. Ageing Dev. 65, 17–33.
Zaczek, D., Hammond, J., Suen, L., Wandji, S., Service, D., Bartke, A., Chandrashekar, V., Coschigano, K., Kopchick, J., 2002. Impact of growth hormone resistance on female reproductive function: new insights from growth hormone receptor knockout mice. Biol. Reprod. 67, 1115–1124.
Zhao, Y.Y., Wu, S.P., Liu, S., Zhang, Y., Lin, R.C., 2014. Ultra-performance liquid chromatography-mass spectrometry as a sensitive and powerful technology in lipidomic applications. Chem. Biol. Interact. 220, 181–192.
Zhou, J., Zhong, Q., Li, G., Greenberg, M.L., 2009. Loss of cardiolipin leads to longevity defects that are alleviated by alterations in stress response signaling. J. Biol. Chem. 284, 18106–18114.
Zhu, M., Miura, J., Lu, L.X., Bernier, M., Decabo, R., Lane, M.A., Roth, G.S., Ingram, D.K., 2004. Circulating adiponectin levels increase in rats on caloric restriction: the potential for insulin sensitization. Exp. Gerontol. 39, 1049–1059.
Zieba, D.A., Amstalden, M., Williams, G.L., 2005. Regulatory roles of leptin in reproduction and metabolism: a comparative review. Domest. Anim. Endocrinol. 29, 166–185.