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REVIEW ARTICLE

Lipidomics in longevity and healthy aging

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Abstract The role of classical lipids in aging diseases and human longevity has been widely acknowledged. Triglyceride and cholesterol concentrations are clinically assessed to infer the risk of cardiovascular disease while larger lipoprotein particle size and low triglyceride levels have been identified as markers of human longevity. The rise of lipidomics as a branch of metabolomics has provided an additional layer of accuracy to pinpoint specific lipids and its association with aging diseases and longevity. The molecular composition and concentration of lipid species determine their cellular localization, metabolism, and consequently, their impact in disease and health. For example, low density lipoproteins are the main carriers of sphingomyelins and ceramides, while high density lipoproteins are mostly loaded with ether phosphocholines, partly explaining their opposing roles in atherogenesis. Moreover, the identification of specific lipid species in aging diseases and longevity would aid to clarify how these lipids alter health and influence longevity. For instance, ether phosphocholines PC (O-34:1) and PC (O-34:3) have been positively associated with longevity and negatively with diabetes, and hypertension, but other species of phosphocholines show no effect or an opposite association with these traits confirming the relevance of the identification of molecular lipid species to tackle our understanding of healthy aging and disease. Up-to-date, a minor fraction of the human plasma lipidome has been associated to healthy aging and longevity, further research would pinpoint toward specific lipidomic profiles as potential markers of healthy aging and metabolic diseases.

Keywords Lipidomics · Longevity · Healthy aging · Sex differences · Metabolic syndrome

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Introduction

The apparent role of lipids in human health, disease, and aging has intensified scientific research seeking to associate metabolic diseases with specific lipid species to understand its biological basis and develop preventive or therapeutic strategies.

Currently, a typical lipid profile for clinical use consists of plasma measurements of cholesterol and triglyceride (TG) concentrations while a more detailed profile would also consider levels of major lipoproteins. These information is generally used to assess lipid disorders and the risk for metabolic diseases such as hypertension and diabetes. The concomitant use of clinical lipids and genetic markers have not fully

succeeded to predict disease risk or health states. This has potentiated large-scale studies of pathways and networks of metabolites in biological systems giving rise to the field of lipidomics (Gross and Han 2011) as a branch of metabolomics. The application of metabolic profiling strategies to identify and quantify entire lipid categories in plasma will allow in the near future the use of a lipid or metabolic profile as a marker of health, disease, therapeutic efficacy, or for finding novel drug targets. In this regard, high TG levels are linked to an increased risk of cardiovascular disease and metabolic syndrome, and lipidomic profiling has shown that not all molecular TG species associate with its deleterious health effects. For example, TG (54:6), has emerged from epidemiological studies as a link to obesity, BMI, and subcutaneous fat (Pietilainen et al. 2007). In addition, TG (54:6) has been recently associated with human longevity and type2 diabetes. Another interesting example is represented by phosphocholines which may be intermediates of the proximal cause of heart disease, as recent investigations have shown that dietary phosphocholines are metabolized in the gut microbiota into trimethylamine (TMA), which is in turn absorbed into the bloodstream and transformed to atherogenic trimethylamine-*N*-oxide (TMAO) after hepatic metabolism (Loscalzo 2013). Alteration in plasma phosphocholine concentrations has been found in hypertension, obesity, diabetes, and healthy aging (Pietilainen et al. 2007; Graessler et al. 2009; Suhre et al. 2010; Gonzalez-Covarrubias et al. 2013), but molecular species of phosphocholines metabolized to TMA by the gut microbiota have not been investigated thus, the link between dyslipidemias and gut metabolism has yet to be determined. This highlights the importance of characterizing individual lipid species that can provide better diagnostic and prognostic molecular markers. Here, we will focus on a small fraction of the human plasma lipidome that has been associated with human longevity and aging diseases.

Plasma lipid diversity

The human plasma lipidome is composed of thousands of different lipids, whose diversity in function is only paralleled by its wide variation in structure (Quehenberger et al. 2010). The current increase of patients with lipid-related disorders demands a more detailed lipid analysis to pinpoint major classes and molecular species connected with signaling pathways in health and disease (Wang et al. 2011; Sugiyama and Agellon 2012).

Some of the first efforts to comprehensively characterize the lipid diversity of human plasma were carried out using mass spectrometry techniques (Quehenberger and Dennis 2011). Preliminary results have hinted to an estimate of thousands of different lipid species in mammalian cells (Dennis 2009). The LIPID MAPS initiative in lipidomics, has defined eight categories of lipids and several lipid classes and subclasses to promote the use of a consistent reference to lipid molecular species (Table 1). The goal of lipidomics is to identify and characterize all of the lipid species in a cell, tissue, or organism although it is still difficult given the wide physico-chemical differences of lipid species which hampers their simultaneous characterization by analytical techniques (Fahy et al. 2005). Currently, it is possible to identify and characterize a few hundreds of lipid species at once using mass spectrometry (Gross and Han 2011).

Lipid genes and longevity

Human exceptional longevity is the outcome of a complex interplay between genetic and environmental influences with the latter mostly seen in the metabolic

Table 1 Lipid classes in human plasma

Lipid category	Example	Subclasses	Number of species[a]
Fatty acids	Linoleic acid	2	107
Glycerolipids	Triglycerides	3	73
Glycerophospholipids	Phosphocholines	9	160
Sphingolipids	Sphingomyelins	4	204
Sterol lipids	Cholesterol	2	36
Prenol lipids	Coenzyme Q	2	8

[a] Estimated number of species in human plasma

phenotype. The ultimate goal of the quest for longevity genes is to identify genotypes, phenotypes, and environmental influences on human aging. It has been estimated that the hereditary component of human longevity is about 20–35 % (Mitchell et al. 2001; Crimmins and Finch 2012). Genomics has been thoroughly seeking for genes that can explain variations in human maximum lifespan, but longevity-associated genes often have a pleiotropic effect hence, the difficulty to identify a group of genes that can explain some or most of the interindividual variation in lifespan. Longevity candidate loci include genetic variants on insulin, insulin-signaling, immune response, telomere length, oxidative status, DNA repair, and lipoprotein metabolism (Budovsky et al. 2013; Deelen et al. 2013). The loci for APOE and FOXO3A are the most widely studied and validated as longevity loci in different population cohorts. Interestingly, numerous genes associated with longevity are also involved in lipid metabolism (Tacutu et al. 2010). For example, apolipoprotein CIII variant, APOC3 C(-641)V, correlates with a favorable lipoprotein particle size and serum levels (Atzmon et al. 2006), ApoE, essential for the catabolism of TG rich lipoproteins constituents, has been reported to be linked to lifespan in several cohorts (Nebel et al. 2011; Sebastiani et al. 2012). The ε4 allele on *APOE,* present in ~14 % of the population, has been associated with early mortality; while the joint effect of ApoE ε4 and ε2 alleles, explain a larger proportion of the variation in human longevity (Schupf et al. 2013). Other examples of longevity genes involved in lipid metabolism and signaling are cholesterylester transfer protein (CETP; rs9923854), interleukin-6 (IL6; rs2069827), ceramide synthase (CerS), homolog of the longevity assurance gene (LAG1) in yeast, adiponectin variant ADIPOQ (+2019 del) (Atzmon et al. 2008), and lipoprotein lipase (LPA) (Bergman et al. 2007; Soerensen et al. 2013), but the molecular mechanisms by which of these variants influence longevity have not been reported (Sebastiani et al. 2012; Beekman et al. 2013). Current investigations have expanded their quest towards the identification of protective and buffering genes (Bergman et al. 2007). Ongoing next generation sequencing (NGS) and OMIC approaches are likely to identify the joint effect of genetic variants and metabolic profiles to better understand this complex phenotype (Barzilai et al. 2003; Martin et al. 2007).

Plasma lipidomics and familial longevity

Studies of centenarians, nonagenarians, and their offspring have given clues to the biochemistry and pool of molecules involved in aging. The design of the Leiden longevity study (LLS) and other similar family-based cohorts allows to investigate the offspring of nonagenarians, a group genetically enriched for longevity, and compare it to age-match controls (Schoenmaker et al. 2006). These investigations have shown that human longevity is characterized by a favorable lipid metabolism, lower prevalence of insulin resistance, hypertension, and cardiovascular disease (Barzilai et al. 2001; Atzmon et al. 2004; Schoenmaker et al. 2006; Westendorp et al. 2009). Detailed lipid investigations showed that total TG levels, and particle size of high density lipoprotein (HDL), and low density lipoprotein (LDL) associate with human familial longevity and healthy aging (Barzilai et al. 2003; Heijmans et al. 2006). Interestingly, LDL particles are the main carriers of sphingomyelins and ceramides, while ether phosphocholines are mainly present in HDL particles, partly explaining their opposing roles in atherogenesis. This suggests that specific lipid species and lipoprotein metabolism may play unique roles in healthy aging (Nelson et al. 2006; Yeboah et al. 2010).

Investigations within the LLS cohort have shown that longevity can be gender specific, (Vaarhorst et al. 2011) identified that plasma TG levels are associated with longevity only in females, adding a level of complexity to the trait. More recently, using a lipidomic targeted approach a profile of nineteen lipid species was associated with familial longevity in the offspring of nonagenarians, consisting of six sphingomyelin, one phosphoethanolamine, four phosphocholines, and six TGs species (Gonzalez-Covarrubias et al. 2013) (Table 2).

A longevity lipidomic profile and healthy aging

Results from metabolic profiling studies have sought to associate metabolite levels and profiles to a certain phenotype. In the LLS the plasma lipidomic profile was associated to longevity, type 2 diabetes, and hypertension. Below, it is discussed the potential health implications of the above mentioned lipidomic profile. First, longevity-associated sphingomyelin species were also positively associated to type 2

Table 2 Lipidomic profile associated with familial longevity in females

Lipid	Difference[a]	*P* value	Lipid	Difference[a]	*P* value
PC (O-34:3)	Higher	6.1×10^{-4}	SM (d18:1/21:0)[b]	Higher	8.9×10^{-5}
PC (O-34:1)	Higher	2.7×10^{-4}	SM (d18:1/23:1)[b]	Higher	5.6×10^{-4}
PC (O-36:3)[b]	Higher	2.0×10^{-4}	SM (d18:1/23:0)	Higher	4.9×10^{-3}
PC (O-36:2)[b]	Higher	1.4×10^{-5}	TG (52:1)	Lower	2.0×10^{-3}
PE (38:6)	Lower	3.2×10^{-3}	TG (54:7)	Lower	1.4×10^{-3}
SM (d18:1/14:0)[b]	Higher	1.4×10^{-4}	TG (54:6)	Lower	9.7×10^{-4}
SM (d18:1/15:0)[b]	Higher	2.8×10^{-5}	TG (56:7)	Lower	3.3×10^{-3}
SM (d18:1/16:0)	Higher	2.8×10^{-3}	TG (56:6)	Lower	1.7×10^{-3}
SM (d18:1/17:0)	Higher	3.6×10^{-3}	TG (57:2)	Lower	6.9×10^{-4}
SM (d18:1/18:2)	Higher	5.0×10^{-3}			

[a] Higher or lower in offspring compared to controls

[b] Lipid species associated with familial longevity independent of total triglycerides

diabetes and hypertension, suggesting that higher levels of certain SM species such as SM (d18:1/18:2) and SM (d18:1/17:0) have a positive influence on healthy aging. In agreement, low levels of SM species have been associated with neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's (Piccinini et al. 2010), and with metabolic disorders such as diabetes (Suhre et al. 2010), subclinical atherosclerosis, (Nelson et al. 2006), and cardiovascular disease (Holland and Summers 2008). In addition, the recent association between coffee drinking and lower risk of death by cardiovascular disease and diabetes maybe explained in part by an increase of several SM species during coffee consumption (Freedman et al. 2012; Altmaier et al. 2009). Although the health implications of higher levels of SM species in the offspring of long-living individuals remains to be investigated, it is possible that higher levels of SM species in female offspring of nonagenarians are a consequence of decreased SMase activity maybe decreasing the risk of ceramide-related diseases. Another possibility is that higher levels of SM species may be compensating for the deleterious increase of TG with age in females since SM levels increase with age in all women, but in women prone to longevity SM levels are consistently higher.

Ether phosphocholine species prevent oxidation of polyunsaturated fatty acids in lipoproteins, a feature suggested as sex-dependent (Helmy et al. 2003; Wiesner et al. 2009). In the LLS, a youthful profile was associated with higher levels of ether PC species including PC (O-34:3) and PC (O-34:1), which seems consistent with their antioxidant and cardioprotective roles. Accordingly, down regulation of several ether phospholipids is linked to the prognosis of hypertension and diabetes (Graessler et al. 2009; Suhre et al. 2010). Thus, it is possible that higher levels of ether phosphocholines associated to longevity reflect a better antioxidant capacity and a healthier lipid profile compared to that of controls.

Phosphoethanolamine species, the second most abundant membrane phospholipid in mammals, have been identified as modulators of inflammation and apoptosis (Gibellini and Smith 2010), but little is known about specific molecular species. Lower levels of phosphoethanolamine, PE (38:6), have been associated with longevity. This is a highly polyunsaturated phospholipid that can be easily oxidized and bear different acyl chains including proinflammatory precursors. Lower levels of this particular PE may offer a less oxidative environment or a lower prevalence of inflammatory-related molecules such as arachidonic acid (C20:4) in women prone to longevity. Conclusive hypotheses around PE (38:6) however, may be generated after completion of the detailed stereochemistry of the fatty acyls attached to this lipid.

A plethora of studies have linked high TG levels to the development of atherogenesis and cardiovascular disease (Coen et al. 2010; Boullart et al. 2011), and accumulation of long-chained TGs are also associated with loss of insulin sensitivity (Kamath et al. 2011). Moreover, total TG concentrations increase significantly with age in women after menopause contributing to a detrimental health status with increasing age

(Sugiyama and Agellon 2012). Nevertheless, the molecular characterization of individual TG molecules involved in atherogenesis and lipid changes associated with menopause remains elusive (Schwartz and Reaven 2011). Investigations of a fraction of the plasma lipidome in the LLS identified four long-chained and highly polyunsaturated TG species, TG (54:7), TG (54:6), TG (56:7), TG (56:6), associated with human longevity. Lower levels of polyunsaturated TG species in long-living individuals may reflect an efficient beta-oxidation function, a tendency that may be opposing the effects of age and menopause.

The MUFA–PUFA ratio and the oxidative stress theory of aging

Dyslipidemias and dysfunctional fat tissue appears to accelerate the onset of multiple age-related diseases, while interventions that delay or limit fat tissue turnover, redistribution, or dysfunction are associated with enhanced health and maximum lifespan (Crimmins and Finch 2012). The oxidative stress theory of aging states that the generation and accumulation of reactive oxygen species (ROS) are responsible for the progressive deterioration of the macromolecules within the cell. The source of this damage is mainly posited in the "leak" of ROS during aerobic metabolism by the mitochondria. In fact, ROS levels seem to correlate with lifespan (Buffenstein et al. 2008). Although ROS are molecular messengers and have numerous roles in cell signaling (Dowling and Simmons 2009) their accumulation or limited scavenging by antioxidants contribute to the deterioration of proteins, DNA, and lipids. Mitochondrial enzymatic activity is embedded in membrane bilayers making them the first target for ROS attack. Highly polyunsaturated lipids are particularly susceptible to this attack i.e. saturated and monounsaturated fatty acyl chains (SFA and MUFA) are essentially resistant to peroxidation, while polyunsaturated fatty acyl chains (PUFA) are easily damaged and the greater the degree of polyunsaturation, the more prone to peroxidative damage. Moreover, lipid peroxidation does not end in lipid detriment, but oxidized lipids are a source of damage to other macromolecules and adduct formation since the oxidized lipid is a radical itself (Hulbert 2003). These end-products of lipid peroxidation are in addition mutagenic and carcinogenic thus, the removal of lipid hydroperoxides may be key to the onset of aging diseases (Muller et al. 2007). Thorough investigations on lipid bilayers and lifespan by Hulbert et al. have shown that a higher MUFA-to-PUFA ratio is associated with lower lipid peroxidation, oxidative damage, and maximum lifespan. Therefore, variation in membrane lipid composition directly influence oxidative damage and lifespan across many mammalian species (Hulbert 2005). The relationship between lower membrane unsaturation and larger lifespan has been established for membranes of different tissues and animal species (Pamplona et al. 2000; Portero-Otín et al. 2001).

In humans, Puca et al., found that erythrocyte membranes of nonagenarian offspring have a higher content of monounsaturated fatty acids and lower levels of polyunsaturated fatty acids compared to controls, suggesting that cellular membranes of individuals prone to longevity have a different lipid composition (Caprari et al. 1999; Puca et al. 2007). Viviani Anselmi et al. (2010) reported that, membranes of red blood cells with a lower PUFA-to-MUFA ratio are associated with a healthier heart are because of lower lipid peroxidation. Within the LLS, we reported a 9.2 % higher MUFA-to-PUFA ratio associated with longevity. Together these observations expand the notion that a low PUFA-to-MUFA ratio is part of another lipid-related mechanism underlying human longevity and healthy aging. A higher proportion of monounsaturated over polyunsaturated lipids may be indicative of a metabolic shift towards a lower synthesis or absorption of polyunsaturated fats or a higher clearance of highly peroxidable lipids. This phenomenon has been suggested as indicative of a homeoviscous membrane adaptation in which higher levels of monounsaturated lipids maintain membrane fluidity and function while lowering the generation of oxidative species, this tends to be specific for each animal species and hence, enzymes of membrane remodeling are likely to be genetically regulated contributing to the hereditability of lipid metabolism and longevity (Hulbert 2008).

Sexual dimorphism in lipid metabolism

Gender-related differences have been identified for several features related to lifespan including genetic variants (Slagboom et al. 2011), telomere length (Cherif et al. 2003; Broer et al. 2013), incidence of metabolic diseases (Lie et al. 2006), and lipid metabolism (Vaarhorst et al. 2011). For example, the

val-allele on methylenetetrahydrofolate reductase, a key enzyme in the methylation of homocysteine, has been correlated with cardiovascular disease and increased mortality in elderly men, but not in women (Heijmans et al. 1999). In females, many genes can escape X-inactivation enabling women to have two functional alleles and a striking heterogeneity in gene expression patterns. In agreement, women lacking an X-chromosome (Turner Syndrome) present a greater risk for developing metabolic syndrome, high TGs, and LDL concentrations, indicating that the sex chromosome complement affects blood lipids independently of hormone secretion. A metabolomic-GWAS study based on a large epidemiological cohort, showed that metabolite profiles and genetic variants are significantly different between males and females (Mittelstrass et al. 2011).

Many factors can contribute to sex differences in lipid metabolism and its association with longevity, including risk of cardiovascular disease (CVD), visceral fat, abundance of peroxisome proliferator-activated receptor alpha (PPAR-alpha), and sterol regulatory element-binding protein-2 (SREPB-2) all of which are higher in males. In contrast, proportion of total fat distribution, subcutaneous fat, insulin sensitivity, leptin concentrations, LPA activity, free fatty acid appearance in plasma, VLDL clearance, and fatty acid binding proteins (FABPs) are higher in females. Lack of FABP1 significantly increases the incorporation of fatty acids into TG in females and decreases beta-oxidation of fats in males, thus causing fatty liver in males and larger TG deposits in females. Some studies have shown that women have higher expression of beta-oxidation genes and that male and female differences in lipid metabolism can be partly explained by differences in expression of proteins involved in lipid oxidation (Mittendorfer 2005). Some highly polluted regions have reported higher female than male births thus, it is possible that hydrophobic environmental pollutants accumulate in adipose tissue and that X-linked genes regulate lipid metabolism conferring enhanced survival of females (Sugiyama and Agellon 2012).

After menopause, women display an important increase in visceral fat and total TGs, so that their risk of CVD parallels that of men (Miller et al. 2011; International Consortium for Blood Pressure Genome-Wide Association Studies 2011). Analysis of metabolic profiles after stratification of women before and after menopause, may offer some clues since genetic variants distinctively affect each population. For instance, the XbaI A-to-G polymorphism on the estrogen receptor alpha is linked to increased body mass in premenopausal but not in postmenopausal women or in men, despite the fact that men with higher BMI produce higher estrogen levels (Okura et al. 2003). Visceral fat is synthesized at higher rates in women with increasing age via aldehyde dehydrogenase 1a1 (Aldh1a1) and retinoic receptor, the latter being repressed by high estrogen levels in premenopausal women. Interestingly, an increase of Adh1a1 and visceral fat is observed in climacteric women, but not in men an observation independent of retinoic receptor concentrations, further confirming sex-specific differences in mechanisms that drive visceral adiposity (Yasmeen et al. 2013).

Longevity studies have also shown metabolic differences between males and females. For example, within the LLS, N-glycan profiles associate with longevity distinctively in men and women (Ruhaak et al. 2010; Ding et al. 2011), total TG concentrations are a marker of familial longevity only in females, and, lipidomic profiling revealed a lipid profile of 19 lipid species as determinants of female, but not male, familial longevity (Table 2). Classical lipid differences between males and females have long been recognized, but lipid differences between sexes at the molecular level have been rather limited. For example, it is well known that total TG concentrations are higher in men than in women. However, the plasma lipidome contains tenths of different TG species that constitute the parameter of total TG and it is not clear which TG species contribute to increased CVD risk (Quehenberger et al. 2010; Quehenberger and Dennis 2011). Lipidomic profiling and sex stratification studies within the LLS provided in-depth gender differences including a lipid profile associated to familial longevity in females only and significantly higher levels of TG (52:1) and TG (54:6) in males compared to females. All the above confirms and expands the fundamental sex differences in the ability to mobilize and oxidize intracellular lipids and points out the importance of considering male and females as separate entities in the evolution of dyslipidemias, lipid metabolism, metabolic diseases, and processes leading to healthy aging and longevity. The massive identification of metabolites in health and disease in large epidemiological settings has helped to depict

differences between males and females preparing the necessary tools to address their health and longevity in a sex-dependent manner.

Lipidomics in aging and metabolic diseases

The association between fatty acids, fat tissue, lipid profiles, human longevity, and healthy aging has been repeatedly reported throughout the last decade (Barzilai et al. 2001; Atzmon et al. 2004; Vaarhorst et al. 2011). Individuals prone to longevity show favorable lipid profiles (Heijmans et al. 2006; Deelen et al. 2011; Schupf et al. 2013), accompanied by a lower incidence of metabolic syndrome (van Heemst et al. 2005; Euser et al. 2008; Pawlikowska et al. 2009; Rozing et al. 2009; Rozing et al. 2010; Barzilai et al. 2012) and aging diseases such as Alzheimer's (Westendorp et al. 2009; Lipton et al. 2010; Han et al. 2011). The disposition of lipids in the body and its health consequences maybe even suggesting a role for dietary lipids in healthy aging (Puca et al. 2008; Abbott et al. 2012). Aging diseases and longevity encompass complex metabolic features that may gain some insight from the increasing research on lipidomics and other OMIC fields to describe the metabolic networks of these phenotypes. In the last few years, metabolomics has succeeded generating a vast amount of metabolites and suggesting the role of dozens of lipid species in aging diseases. The molecular characterization of TG and sphingomyelin species has pinpointed specific lipids underlying insulin resistance (Suhre et al. 2010; Rhee et al. 2011), Alzheimer's (Han et al. 2011), hypertension (Graessler et al. 2009), and obesity (Pietilainen et al. 2007). Several research groups worldwide have undertaken the task of dissecting the lipidome of tissue and plasma creating a pool of potential metabolic markers. For example, low levels of phospholipids including phosphocholine PC(20:4) and sphingomyelin SM (d18:1/14:0) have been observed in patients with diabetes (Suhre et al. 2010). Similarly, long-chain sphingomyelins (ej. SM d18:1/22:1) showed a decrease, with a synchronized increase of their corresponding ceramides, in patients with Alzheimer's (Han et al. 2011). Recently, a set of three metabolites including the lipid, lysophosphatidylcholine (18:2), were reported as predictors of preclinical insulin resistance, which led the authors to propose that the conjunct use of these metabolites may offer a decade of preventive efforts to ameliorate the preclinical state of type 2 diabetes before pharmaceutical intervention is needed (Wang-Sattler et al. 2012). Interestingly, lipids of the same class may have opposing associations for insulin resistance including specific TGs, sphingolipids, (Rhee et al. 2011), free fatty acids, phosphocholines (Suhre et al. 2010), and ceramides (Haus et al. 2009), but when considering individual lipids potential inconsistencies unravel, stressing the significance of current endeavors directed toward the molecular characterization of the human lipidome. Table 3 summarizes the molecular lipid species that have been associated to type 2 diabetes.

Table 3 Lipid species associated with risk of type 2 diabetes

Lipid	Risk of diabetes[a]	References
TG (52:1)	Higher	Rhee et al. (2011)
TG (50:0)	Higher	Rhee et al. (2011)
TG (44:1)	Higher	Rhee et al. (2011)
TG (46:1)	Higher	Rhee et al. (2011)
TG (48:0)	Higher	Rhee et al. (2011)
TG (48:1)	Higher	Rhee et al. (2011)
PC (34:2)	Higher	Rhee et al. (2011)
PC (36:2)	Higher	Rhee et al. (2011)
Long chain PUFA	Higher	Suhre et al. (2010)
Total TG	Higher	Suhre et al. (2010)
TG (56:9)	Lower	Rhee et al. (2011)
TG (58:10)	Lower	Rhee et al. (2011)
TG (60:12)	Lower	Rhee et al. (2011)
PC (38:6)	Lower	Rhee et al. (2011)
PC (O-34:3)	Lower	Gonzalez-Covarrubias et al. (2013)
PC (O-34:1)	Lower	Gonzalez-Covarrubias et al. (2013)
LPC (22:6)	Lower	Rhee et al. (2011)
SM (d18:1/23:1)	Lower	Gonzalez-Covarrubias et al. (2013)
SM (d18:1/16:0)	Lower	(Gonzalez-Covarrubias et al. 2013)
Medium chain SFA/MUFA	Lower	Suhre et al. (2010)
Ceramide (22:0)	Higher	Haus et al. (2009)
Ceramide (18:0)	Higher	Haus et al. (2009)
Ceramide (20:0)	Higher	Haus et al. (2009)
Ceramide (24:0)	Higher	Haus et al. (2009)

[a] Depending on the study, risk of type 2 diabetes was determined by linear regression analysis, Pearson correlation, or HOMA-IR test

Investigation of the cellular roles and tissue localization of lipid species associated with longevity, would be the next step towards the understanding of the mechanisms underlying healthy aging and human longevity.

Lipidomics as part of metabolomics seeks to generate a platform of accurate biomarkers that aid in the diagnosis, therapeutics, and prognosis of longevity and aging diseases. In a world where a relevant fraction of our population is approaching 65 years of age it is of commanding relevance the identification of useful markers of longevity and healthy aging in men and women.

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