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ScienceDirect
The International Journal of Biochemistry & Cell Biology 40 (2008) 324–333
IJBCB
www.elsevier.com/locate/biocel

Lipid metabolism and diet: Possible mechanisms of slow aging

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Received 13 March 2007; received in revised form 2 April 2007; accepted 3 April 2007
Available online 8 April 2007

Abstract

The ability to survive to an extremely old age is a consequence of complex interactions among genes, environment, lifestyle and luck. In the last two centuries, life expectancy in western countries has doubled, increasing from 40 to 81 years (79 for males and 82 for females). The candidate factors to determine such mortality reduction are reduced exposure to infections and the subsequent reduction in inflammatory responses, and to some extent, improvement in diet and nutrition.

Among the people born at the beginning of the previous century, a small portion of individuals (1 in 10,000 born) have reached 100 years, surviving approximately 20 years more than the general population. The successful longevity of these individuals shows a familial component, possibly genetic, as underlined by the centenarian sibling's increased chance of reaching 100 years of age compared to the general population.

Genetic studies on long living individuals have led to the discovery of potential genetic causes of extreme longevity. These discoveries have highlighted the role of lipid metabolism as a potential key player in the ability to survive to extreme old age. Additional studies on the longevity phenotype have confirmed the role of lipids and lipid-associated cell activities in the predisposition to longevity, from lower eukaryotes to humans.

The main focus of this review is the appreciation of demographic survival data and changes in recent diet with the above mentioned genetic and phenotypic biomarkers of longevity, in order to elucidate hypotheses on mechanisms of slow aging and disease resistance.

Keywords: Longevity; Aging; Fatty acids; Mild stress; Metabolism

1. Introduction

The relevance of lipids, not only as structural components of cell membranes but in particular as signalling molecules for initiating cellular processes, has attracted a great amount of interest in recent years. Despite the fact that lipid research dates back several decades, the advances of analytical techniques and the use of interdisciplinary approaches are only now allowing new insights into lipid characterization and function. In particular, many groups are working towards the aim of providing a comprehensive view of lipid structures and functions for each organism, at a genomic as well as at the pro-

Abbreviations: APOE, apolipoprotein E; APOC, apolipoprotein C; APOA, apolipoprotein A; CETP, cholesteryl ester transfer protein; LDL, low density lipoprotein; HDL, high density lipoprotein; MTP, mycrosomial transfer protein; FA, fatty acid; SFA, saturated fatty acid; MUFA, mono unsaturated fatty acid; PUFA, poly unsaturated fatty acid; e-nos, endothelial-nitric oxide synthase; NO•, nitrate; ROS, reactive oxygen species; ALA, alpha-linolenic acid; LAC1, longevity-assurance gene cognate 1; TRAM, (Trif)-related adaptor molecule; HSP, heat shock protein; ABCA, ATP-binding-cassette A

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doi:10.1016/j.biocel.2007.04.003

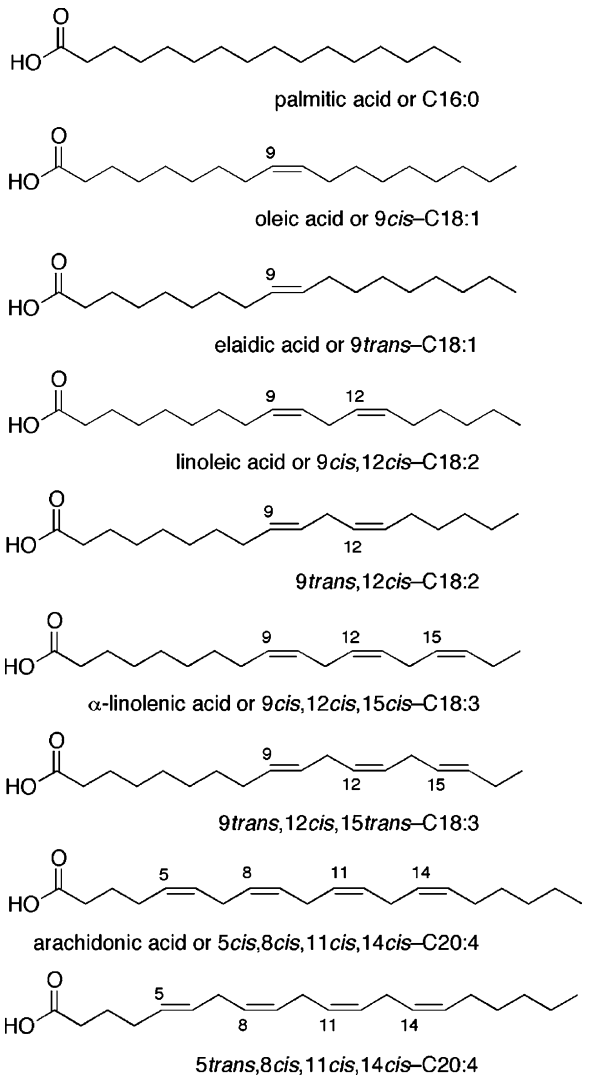

Fig. 1. Examples of common names of natural fatty acids and adopted abbreviations to describe the number of carbon atoms, position and geometry of double bonds.

teomic level (Feng & Prestwich, 2006; Rapaka, Hla, & Dey, 2005).

Several studies have highlighted the role of membrane lipids in membrane "fluidity" and permeability (Vance & Vance, 2002), features also considered by the biomimetic models of liposomes. These two parameters are very much influenced by three types of fatty acid residues present in the membrane: saturated, monounsaturated and polyunsaturated fatty acids. (SFA, MUFA and PUFA). PUFA can be of the omega (ω) or *n* series and can be further distinguished by two distinct families, ω-6 (or *n*-6) and ω-3 (*n*-3). Some examples of mono- and polyunsaturated fatty acid (MUFA and PUFA) structures and some *trans* isomers are shown in Fig. 1. Included in this figure are the common names and the abbreviations describing the position and geometry of the double bonds (e.g., 9*cis* or 9*trans*), as well as the notation of the carbon chain length and total number of unsaturations (e.g., C18:1). The IUPAC nomenclatures presenting the length of the carbon atom chain, the number and the position of double bonds are coupled with trivial/common names, when available, that are still largely used in lipid chemistry and biochemistry. Recently, an initiative for a comprehensive lipid classification has been undertaken (Fahy et al., 2005).To date, an emphasis has been made to characterise the geometry of the ubiquitously found *cis* lipids, and in the case of PUFA, on the double bonds with the characteristic methylene-interrupted motif. It is well known from thermodynamics that *cis* are less stable than their corresponding *trans* isomers, and isolated are less stable than conjugated polyenes. However, all activities of MUFA and PUFA derivatives are based on these two structural features. In particular, the *cis* geometry is provided by the regiospecific and stereoselective enzymatic activity of desaturases (Vance & Vance, 2002). The two features can be compromised by the action of free radicals, with the well known process of lipid peroxidation with formation of oxidized lipids (Rikans &Hornbrook, 1997), and the recently discovered process of lipid isomerization with the formation of *trans* geometrical lipids (Ferreri & Chatgilialoglu, 2005; Chatgilialoglu & Ferreri, 2005).

In Fig. 2, the transformations of linoleic (ω-6 precursor) and linolenic (ω-3 precursor) acids are shown. It is worth recalling that both compounds are essential fatty acids for mammals, and are derived from the precursors of the omega-6 (or *n*-6) and omega-3 (or *n*-3) fatty acid series in food.

Evidence has demonstrated a need for balance between polyunsaturated omega-6 and omega-3 fatty acids in membranes for their correct functioning, but also for general maintenance of the whole cellular machinery. Considering lipids with the same polar head and fatty acid chain lengths, a general rule regulating lipid assembly is that the lower the number of the double bonds, the higher the packing order of the lipids. Therefore, the rigidity of the lipid assembly follows the order: saturated > *trans*-unsaturated > *cis*-unsaturated. The gross membrane property of "fluidity" and also permeability are in the inverted order, so that *cis*-unsaturated residues make a relevant contribution to keeping the "ideal" values.

2. Recent changes in diet

Our genome is the result of millions of years of evolution during which it has been constantly shaped

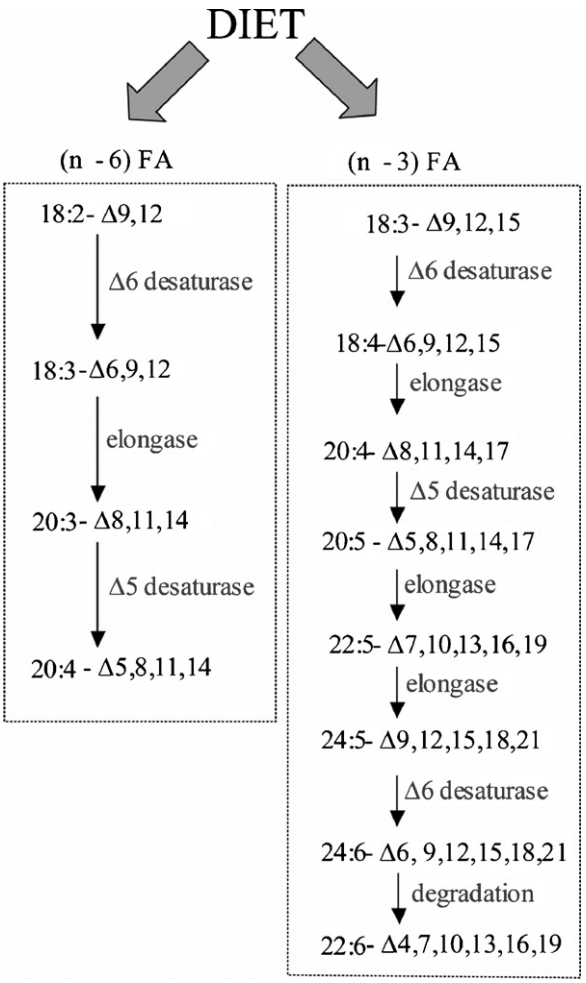

Fig. 2. Major pathways of omega-3 and omega-6 fatty acids in animal tissues.

by the environment. The perfect equilibrium between environment and our organism would give us the best chance to reach our maximum life-span in good health. In industrialized countries, we have been able to reduce infections and famine but we are facing other potential challenges, mostly affecting life after reproductive age, such as cardiovascular disease and type 2 diabetes. According to Cordain et al. (2005), this is possibly a side effect of our changes in dietary habits that accelerated 100 years ago. We have shifted our macronutrient composition from proteins to carbohydrates; increased the intake of saturated fatty acids, exogenous trans-fatty acids and omega-6 fatty acids; decreased our omega-3 intake and decreased the intake of micronutrients (e.g., folate, zinc) and potassium (Cordain et al., 2005). These changes, together with a sedentary life-style, have generated the basis for a recent increase of disease incidence such us cancer, osteoporosis and cardiovascular disease. Moreover, it is possible that we are programmed to survive with a much lower amount of food by favouring a genetic makeup that makes us able to efficiently store energy reserves. However, in the condition of food abundance, we are predisposed to obesity and obesity related disease. A deficit of omega-6 fatty acids causes growth retardation, dry skin, fatty deposits in the liver and reproductive failure. Omega-3 fatty acid deficit, on the other hand, induces dysfunction of the central nervous system and impaired vision, while an omega-3 enriched diet has a protective role in cardiovascular disease (see below). So, while food abundance can explain increased life-expectancy, as discussed below, it is also possible that changes in diet have facilitated the occurrence of certain diseases of aging.

3. Demographic changes

Life expectancy for the U.S. 1900 cohort has been estimated at around 51.5 for males and 58.3 for females. Based on the same tables, 5% of the individuals that reach 65 years of age survive to 91 years if males, and 95 years if females. A much smaller proportion is able to reach 100 years. The frequency of centenarians in the industrialized world is 1 in 10.000 people and this number grows every year approaching a frequency of 1 in 5.000 born in the near future (Perls, 2006). Demographers have always tried to estimate a limit of human life-expectancy, but since 1928 the proposed limits have always been exceeded and there is no evidence that we are approaching a plateau. Female life expectancy in industrialized countries has risen 3 months/year for 160 years by scoring a 4 decade increase in life expectancy in the last 16 decades (Oeppen & Vaupel, 2002). The record of life expectancy is for Japanese women that reach an average of 85 years of age (Oeppen & Vaupel, 2002). The male life expectancy also has risen linearly but slowly, increasing the gap with the female life expectancy from 2 to 6 years (Oeppen & Vaupel, 2002). It has to be noted that Japanese women have the highest life-expectancy of industrialized countries possibly because of their unique diet (Sugano, 1996). Similarly, the low incidence of cardiovascular disease in Greenland Eskimos appears to be due to their high intake of seal meat, whale meat and fish (Carroll, 1986). People born before the 20th century in Northern European countries that experienced reduced mortality at young ages, were also experiencing longevity and decline in mortality at old ages. These phenomena are associated with increased adult height selection. Moreover, taller people showed a reduction of early- and late-age mortality. An hypothesis formulated by the authors of this analysis is that this phenomena

is due to reduced exposure to infection and consequent reduction in inflammation. A second possible explanation is that the improvement in diet and nutrition have promoted both height and longevity (Oeppen & Vaupel, 2002).

Cardiovascular disease today is the main cause of death in humans, as it was 250 years ago when human life-expectancy was 40 years. The only difference resides in prevalence of the disease; it is less prevalent among people born at the beginning of 20th century versus people born before 1845 (Fogel, 2004). This shifting of the cardiovascular disease prevalence in a short period of time would favour the theory of a strong environmental/lifestyle factor that influences the frailty towards cardiovascular disease.

4. Evidences of familiar disease resistance patterns among the centenarians and their family members

Among people that are exposed to the same environmental stresses, there are some individuals that have a genetic makeup that predisposes them to live longer. This is indicated by studies that show that:

(1) Longevity clusters in families are clearly inherited, as confirmed by binomial analysis that excludes the possibility of finding so many centenarians, as observed in a single family, by chance even if all the families in the word are scrutinized (Perls et al., 2000).
(2) Centenarian sibling mortality levels is roughly half throughout their life and the centenarian sibling relative risk to reach 100 is 8 (for females) and 17 (for males) times higher than general population (Perls et al., 2002).
(3) The centenarian's offspring show a reduced risk to all-cause mortality (62%), a lower risk of cancer-specific mortality (71%) and an 85% lower risk of coronary disease-specific mortality (Terry, McCormick, et al. 2004; Terry, Wilcox, et al., 2004).
(4) Ninety percent of centenarians were cognitively intact well into their 90s (10), despite Alzheimer Disease affecting approximately 50% of people over 85 years of age and this prevalence continues to increase at even older ages (Hebert et al., 1995).

The centenarians, despite being under the same category of people that have survived approximately 20 years more than average, can be further divided in three categories according to their ability to escape diseases: survivors, delayers and escapers (Perls, 2006).

5. Role of lipids in cell homeostasis, membrane physical properties and aging

While PUFA precursors (C18:2*n*-6 and C18:3*n*-3) are acquired only with diet, SFA are also endogenous, deriving from the activity of elongase enzymes, and are transformed into MUFA by delta-9 desaturase (C16:0 and C18:0 to C16:1*n*-7 and C18:1*n*-9, respectively) (Clandinin et al., 1991). To be noted, delta-9 desaturase activity and consequent MUFA production decreases with aging (Kumar et al., 1999). By changing the physical property of the membrane bilayers membrane fluidity regulates the plasmalemmal Na^+ gradient, mitochondria H^+ gradient, and more generally, through the regulation of the activity of cell membrane-associated proteins, the rate of metabolic activity and reactive oxygen species (ROS) production (ROS production decreased of 70% by dropping the membrane potential of 10 mV) (Miwa & Brand, 2003). The level of peroxidizability of the membrane bilayer is a critical determinant of the severity of cell damage caused by free radicals. The level of membrane peroxidizability is dictated by the amount of the carbon atoms between the –C=C– units found in PUFA, saturated (SFA) and MUFA obviously do not carry such atoms. In response to attack by free radicals, peroxidation generates a strong self-propagating reaction, which causes damage to other molecules (Herrero & Barja, 1997).

These concepts have been summarized in the membrane pacemaker theory of aging that would indicate that high membrane fluidity and low membrane peroxidizability are the optimal membrane conditions for promoting longevity. This theory has been generated from the observation that body mass/maximum life-span in mammal and bird species directly and inversely correlate, respectively, with the membrane levels of C18:1*n*-9 and C22:6*n*-3. This can be explained by the fact that C22:6*n*-3 is 320-fold more susceptible than C18:1*n*-9 to peroxidation, while the latter have fluidity properties as good as the former (Hulbert, 2005).

6. Lipid profiles as biomarker of longevity

The comparison of centenarian's offspring with age-matched controls led to the identification of phenotypic biomarkers of longevity. Serum lipid particle sizes were found associated with longevity in a population of Ashkenazi (Barzilai et al., 2003). Intriguingly, a genetic locus that influences cholesterol concentration in small low-density-lipoprotein (LDL) particles has been identified at chromosome 4q23, near the microsomial transfer protein (MTP) (Rainwater et al., 1999), the same

locus found to influence exceptional longevity (Puca et al., 2001) (see the genetic approaches). In addition, a "longevity syndrome" was described among families with extremely low levels of LDL particles (Glueck, Gartside, Mellies, & Steiner, 1977).

Some reports appeared on the lipid analyses of old populations and centenarians. Lipid composition of erythrocytes and lymphocytes in the elderly can vary (Caprari et al., 1999; Ponnappan, Holley, & Lipschitz, 1996), whereas it remains constant in young subjects (Decsi & Koletzko, 1994). Generally, the polyunsaturated content is reduced indicating a progressive consumption due to oxidative degradation. In the EVA study, an inverse association between cognitive decline and the ratio of *n*-3 to *n*-6 fatty acids in erythrocyte membranes was established in a quite remarkable group in patients (1389) born from 1922 to 1932 (Heude, Ducimetière, & Berr, 2003). Lower content of *n*-3 PUFA and higher contents of stearic acid and *n*-6 PUFA were found. *n*-3 PUFA are known to have beneficial effects on vascular diseases (Bonaa, Bjerve, Straume, Gram, & Thelle, 1990), whereas *n*-6 PUFA are known to give rise to inflammatory mediators therefore enhancing the risk of neuroinflammation, as identified in brain tissue from AD patients (McGeer & McGeer, 2001). Age also influenced the fatty acid composition of adipose tissues, as seen in a large cohort (10,359 men and women) aged 40–59 years, which confirms the decline of delta-6-desaturase activity, a characteristic more evident in women than men (Bolton-Smith, Woodward, & Tavendale, 1997).

7. Genetic associations point to a role of lipids in longevity

Coronary artery disease and other vasculopathies attributed to unfavourable lipid profiles account for a large percentage of human mortality. For these reasons, common genetic variants that impact on the function of lipid metabolism should be expected to impact on human lifespan. In this regard, genetic association studies were performed on centenarians versus controls:

(1) APOE ε 2 and 4 isoforms were previously associated with susceptibility to cardiovascular and Alzheimer disease. When these isoforms were subsequently examined in centenarians it was shown that APOE ε 2 conferred susceptibility while APOE ε 4 conferred resistance to these diseases. This was a consequence of demographic pressure and the lack of detrimental alleles and enrichment of the protective ones as populations age (Lewis & Brunner, 2004).
(2) A sib-pair analysis strategy was adopted to identify a locus at 4q23-26 (Puca et al., 2001) that was subsequently investigated with haplotype based associations on 875 polymorphisms that identified a −493 G/T MTP variant. This variant showed a consistent association in a second group of 250 centenarians and 250 controls selected to minimize the mahalanobis distance with respect to cases to avoid stratification (Geesaman et al., 2003). MTP is thought to be the rate-limiting step in the production of lipoproteins (Jamil et al., 1998).
(3) CETP, for its role in determining lipid particle size, was investigated in an Ashkenazi population. Of the few SNPs tested, CETP I405V polymorphism showed homozygous genotypes for the minor allele strongly associated with longevity (Barzilai et al., 2003).
(4) A recent study on the same Ashkenazi populations identified, among 66 polymorphisms tested that belong to 33 candidate genes, −641 C/A APOC3 homozygous for CC associated with longevity. The CC carriers had lower prevalence of hypertension and greater insulin sensitivity (Atzmon et al., 2006).

8. Endogenous trans fatty acids and longevity

Together with the oxidation of lipids; more recently, it has been indicated that trans geometrical isomers of fatty acids, in particular oleate and arachidonate content, are biomarkers of the occurrence of endogenous isomerization processes at the expense of *cis* geometry displayed by the natural unsaturated fatty acids (Chatgilialoglu & Ferreri, 2005). This isomerization starts from free radical stress conditions, mainly due to radical species in the form of amino acids, peptides and proteins derived from sulfur-containing compounds, which are abundant in the biological environment (Ferreri, Kratzsch, Landi, & Brede, 2005). A specific library allows the trans lipids to be distinguished from those derived from dietary contribution, and several investigations on their role in the lipidome of eukaryotic cells are in progress (Ferreri, Kratzsch, Brede, et al., 2005).

As in the case of exercise (McArdle & Jackson, 2000; Minois, 2000; Mthers, Fraser, McMahon, Saunders, Hayes, & McLellan, 2004; Niki, Yoshida, Saito, & Noguchi, 2005), a rapid change in redox state can trigger an activation of molecular and enzymatic pathways for adaptive responses and increased resistance to stress damage. Thus, increased levels of endogenous trans lipids can ultimately be envisioned to be associated with a predisposition to exceptional longevity (Crawford & Davies, 1994; Demple, 1999).

9. Caloric restriction and longevity

From yeast to primates, calorically restricted animals show an extension of their maximum life-span (Clancy, Gems, Hafen, Leevers, & Partridge, 2002). In humans, long-term caloric restriction influences the biological parameters, which are altered with aging. These include risk factors for atherosclerosis, such as reduction of serum total cholesterol, low density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, high sensitivity C-reactive protein, systolic and diastolic pressure, while other factors like high density lipoprotein (HDL) are increased (Fontana, Meyer, Klein, & Holloszy, 2004). Changes in lipid membrane bilayer profiles (decrease in the C20:4*n*-6/C18:2*n*-6 ratio), that occur under caloric restriction, are associated with reduced peroxidizability (Hulbert, 2005; Laganiere & Yu, 1993). In mice, caloric restriction promotes longevity via induction of e-nos expression, mitochondrial biogenesis and adenosine triphosphate production. These effects were strongly reduced in e-nos null mutant mice (Nisoli et al., 2005). Thus, there are evidences that the molecular stressor $NO^{\bullet}$, an e-nos product that induces trans-fatty acids formation (Kermorvant-Duchemin et al., 2005), is important for caloric restriction mediated lifespan extension.

10. Longevity assurance genes in yeasts

Sphingolipids are a complex class of membrane lipids present in all eukaryotes that form specialized areas in the membrane, referred to as rafts or microdomains. The sphingolipid intermediate ceramide is important for activating and coordinating signaling pathways during mammalian stress responses (Dickson et al., 1997). Moreover, the yeast replicative life span extension is induced by sub lethal heat stress via alterations in sphingolipid metabolism (Jazwinski, 1999).

A deletion in a ceramide synthase called *LAG* (for longevity assurance gene), induced in haploid cells, causes a 50% increase in mean and maximum life span (D'mello et al., 1994) The delay in transport of glycosylphosphatidylinositol-anchored proteins from ER to Golgi, secondary to the defect in ceramide biosynthesis is the likely cause of increased longevity (Barz & Walter, 1999).

LAG1 has a close homologue in yeast (LAC1), and orthologues of these two genes occur in a wide variety of eukaryotic cells (Jiang, Kirchman, Zagulski, Hunt, & Jazwinski, 1998).

LAG1 and *LAC1* have significant sequence similarity to TRAM, a mammalian membrane protein thought to be involved in protein translocation across the ER membrane (Jiang et al., 1998).

Intriguingly, a TRAM gene resides on the human chromosome 4 longevity locus.

Among the various roles of ceramide, it has to be cited that the increase of ABCA1 plasma membrane content and of APOA-I binding, induces a cholesterol efflux with consequent beneficial effects on HDL levels and cardiovascular risk (Witting, Maiorano, & Davidson, 2003).

11. Heat shock proteins as biomarkers of aging

Terry et al. have shown that offspring of centenarians have reduced HSP70 release in their serum (Terry, McCormick, et al. 2004; Terry, Wilcox, et al., 2004; Terry et al., 2006). HSP70 is a chaperone released under stress conditions to mitigate cell damage and a biomarker of inflammation. A possibility is that centenarian offspring have reduced levels of HSP70 as a consequence of their inflammation-free status (Njemini, Demanet, & Mets, 2004). There is a known phenomenon of adaptation to chronic stresses by increasing membrane fluidity that in turn adjusts the threshold level of stress at which HSPs are released (Carratu et al., 1996). In this regard, yeast cells in order to adopt a different stress-point for HSP release, selectively increase the percentage of C16:1*n*-7 in response to high stress conditions (increased salt concentrations in the medium) (Chatterjee, Khalawan, & Curran, 2000). Intriguingly, in worms, the level of activity of the hsp-26.2 promoter predicts as much as a four-fold variation in survival and ability to withstand a subsequent lethal thermal stress (Rea, Wu, Cypser, Vaupel, & Johnson, 2005).

12. Hypothesis on longevity determinants

Based on all the evidence reported above, we have generated some reasonable hypotheses:

(1) Long-living individuals have a genetically determined advantage that alters their lipid metabolism and in turn their basal membrane lipid composition, allowing better cell adaptation to stresses with a consequent delay of disease incidence (onset) and aging. In more detail, a long-living descendant's membrane lipid composition could benefit from the e-nos mediated formation of molecular stressors that, through the generation of endogenous trans formation, induce stress resistance. Moreover, the role of basic stress enhancing the antioxidant and radical defences in the body has been recently

supported by several papers dealing with the idea that low exercise confers adaptive responses (Niki et al., 2005). Mild stress has also been linked to longevity (Minois, 2000). Examples of mild stress are caloric restriction, exercise and cognitive stimulation (Arumugam, Gleichmann, Tang, & Mattson, 2006).

(2) It is possible that long-living individuals carry genetic advantages that mimic the beneficial effects of specific balanced diets as shown by evidence that MUFA and omega-3 PUFA-enriched diets reduce cardiovascular disease incidence. People that eat nuts (high monounsaturated fatty acids content) five times per week have a 50% reduction of cardiovascular disease incidence (Dreher, Maher, & Kearney, 1996; Fraser, Sabate, Beeson, & Strahan, 1992). The EPIC-elderly prospective cohort study, investigated 74.607 men and women and showed a reduced overall mortality among the elderly that assumed a modified Mediterranean diet in which saturated fatty acids were substituted for monounsaturated forms (Trichopoulou et al., 2005) Moreover, recent data show that omega-3 rich diets increase LDL lipid particle size if combined with lowering of triglycerides (Griffin et al., 2006) and large LDL lipid particles are patognomonic of longevity. It is also well documented the important antiarrhythmic effects of omega-3 fatty acids, especially for ventricular ectopy, atrial fibrillation as well as ventricular tachyarrhythmia (Reiffel & McDonald, 2006).

The above mentioned data fit well with the evidence collected by Di Nardo and colleagues that alpha-linolenic acid (ALA)-enriched diet reduces the severity of cardiomiopathy in delta-sarcoglycan knock-out hamsters (Fiaccavento et al., 2006). This cardiomiopathic animal model showed unusual lipogenesis, possibly induced by low levels of insulin, with consequent decreases in C16:1*n*-7 and an increase of C18:2*n*-6 (Vecchini et al., 2001). An ALA-enriched diet was able to induce substantial improvement of myocardial health and an impressive increase of animal survival (Fiaccavento et al., 2006).

Overall, these data point to better diet and nutrition as the cause of the recent increase of North European Caucasian life-expectancy and the associated shift towards older ages of cardiovascular disease prevalence.

Moreover, the above-mentioned animal model points to a low level of arachidonic acid and high levels of MUFA as disease resistance inducers of lipid pattern. How this pattern induces such beneficial effects need to be further investigated. Many hypotheses can be formulated on how the membrane lipid composition influences cellular processes. As an example, the delta-sarcoglycan gene, that is a membrane protein, if mutated, mislocalizes to the nucleus (Heydemann, Demonbreun, Hadhazy, Earley, & McNally, 2007) Additionally, the nuclear protein lamin A was mislocalized throughout the nucleoplasm (Heydemann et al., 2007) as a consequence of a dominant negative effect of the delta-sarcoglycan gene mutation. Based on Di Nardo experiments, it is possible that ALA diet, through its positive effect on the deltasarcoglycanophaty, could also influence lamin A function, an important player in cardiomyopathy and the aging process (Capell & Collins, 2006). Looking at the overall scenario, it is still very difficult to predict what mechanism is involved in such beneficial effects, however, the lipidomics approach can be successfully coupled with studies of other cell domains to obtain a complete description of all the relevant aspects influencing aging.

13. Future prospects

Based on the evidences reported in this review, we are strongly supportive of the role of lipid metabolism in determining the rate of aging and ultimately the chance to reach extreme ages (healthy aging). This is possibly modulated by our endogenous lipid metabolism, lifestyle and, very importantly, our diet.

We would also like to provocatively propose the possibility of increasing human health by carefully modifying the diet and life style, possibly based on personal needs. To accomplish such a goal a new field of nutrilipidomics would need to be initiated, to combine lipid profiles with personalized nutrition. We would expect that a careful analysis of individual fatty acid membrane profiles, and its correction through an ad hoc diet, would result in a huge improvement in the general functioning of cells and consequently in the body health.

14. Conclusions

The tremendous increase of life-expectancy in western countries over the last two centuries, and the recent changes in macro- and micro-nutrient diet content paired with scientific evidences that point to an important role of lipids in diet, makes a strong case in favour of lipid metabolism as a longevity determinant. Lipids are candidates to modulate longevity through various mechanisms, from signalling that activates stress resistance, to regulators of cell membrane-associated protein activities.

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