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Forum

Lipid Profiles and Signals for Long Life

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Historically, fat was considered detrimental to health and lifespan. However, lipidomics, the quantification of all lipid molecules in a biological sample, and genetic studies in model organisms are revealing specific fats that may promote longevity. These emerging findings provide insight into the complex relationship between lipids and longevity.

Lipids and Lifespan

Lipids are essential components of biological membranes, energy sources, and signaling molecules. Lipid signals influence fat synthesis, storage, and catabolism, creating intricate metabolic networks that allow organisms to respond to nutrient availability and energy demands or otherwise adapt to changing environments [1]. Storage lipids (triglycerides) and circulating lipid–protein complexes (lipoprotein particles) have previously been linked to diseases of aging [2], and obesity limits longevity [3]. But can lipids beneficially influence lifespan? Lipid profiles of long-lived humans and model organisms and genetic studies of lipid metabolism suggest that this is the case.

Box 1. Lipid Profiling Challenges and Technologies

Lipids exist in a staggering array of sizes, biophysical properties, and relative abundance. An organism's lipid profile is determined by the combined influences of dietary lipids, *de novo* lipogenesis, and the hundreds of enzymes that modulate the length and desaturation of FA chains and their incorporation into more complex lipid molecules. For example, desaturases convert saturated FA chains to MUFAs (one carbon–carbon double bond) and PUFAs (two or more double bonds) (Figure 1). Lipases liberate FAs from lipid molecules to serve as energy sources or signals or to facilitate transport to other tissues [10]. Current methods utilizing liquid chromatography–mass spectrometry (LC–MS) can detect hundreds of unique lipid species, including novel lipid molecules [13]. Although it is still not possible to detect all types of lipid molecules in a 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 FA chain components can detect differences in FA structure at high resolution, revealing trends in lipid profiles [1,13]. Analysis of metabolites without specifically targeting lipids can also identify some lipid molecules [9].

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 (Box 1). The nematode *Caenorhabditis elegans* has emerged as a powerful model for lipid studies due to the detailed characterization of metabolic pathways and ease of genetic manipulation [4,5]. Despite differences in how lipids are stored and synthesized between worms and mammals [4], some lipid profiles associated with longevity may be conserved, and work with *C. elegans* has uncovered molecular mechanisms relating lipids to lifespan that could be explored in mammals.

Lipid Profiles Associated with Longevity

Several lipidomic studies in humans have revealed trends in lipid composition associated with long life. Total lipids extracted from plasma or isolated from erythrocyte membranes of children of long-lived individuals (nonagenarians or centenarians) contain a higher ratio of monounsaturated (MUFA) to polyunsaturated (PUFA) fatty acid (FA) chains relative to matched controls [2]. An increased MUFA:PUFA ratio may influence lifespan by reducing oxidative stress and damage. All lipids can be oxidized by free radicals but PUFAs are the most susceptible to oxidation [2,6]. Because oxidation of FAs propagates further free radical production, high levels of PUFAs could increase oxidative damage on a much larger scale [6].

Several long-lived mutants in *C. elegans*, including mutants with reduced insulin-like signaling and dietary restriction mimics, also exhibited modestly increased MUFA:PUFA ratios when analyzed for general FA chain composition, with the longest-lived mutants having the highest MUFA:PUFA ratios [6]. These worms, and worms lacking a germline (which are also long lived), express higher levels of enzymes that convert saturated FAs to MUFAs (Δ9 desaturases) [3,6] (Figure 1). Additionally, knockdown of Δ5 desaturase, which produces highly unsaturated FAs, appears to promote oxidative stress resistance and lifespan extension in wild-type worms [6]. These findings support a link between PUFA synthesis, oxidative damage, and aging. In mammals, pathways that influence longevity, including insulin and growth factor signaling, regulate Δ9 desaturase expression [3], suggesting that these enzymes may be important targets of other modes of lifespan extension. Future studies are needed to explore the contribution of FA desaturases and their products to

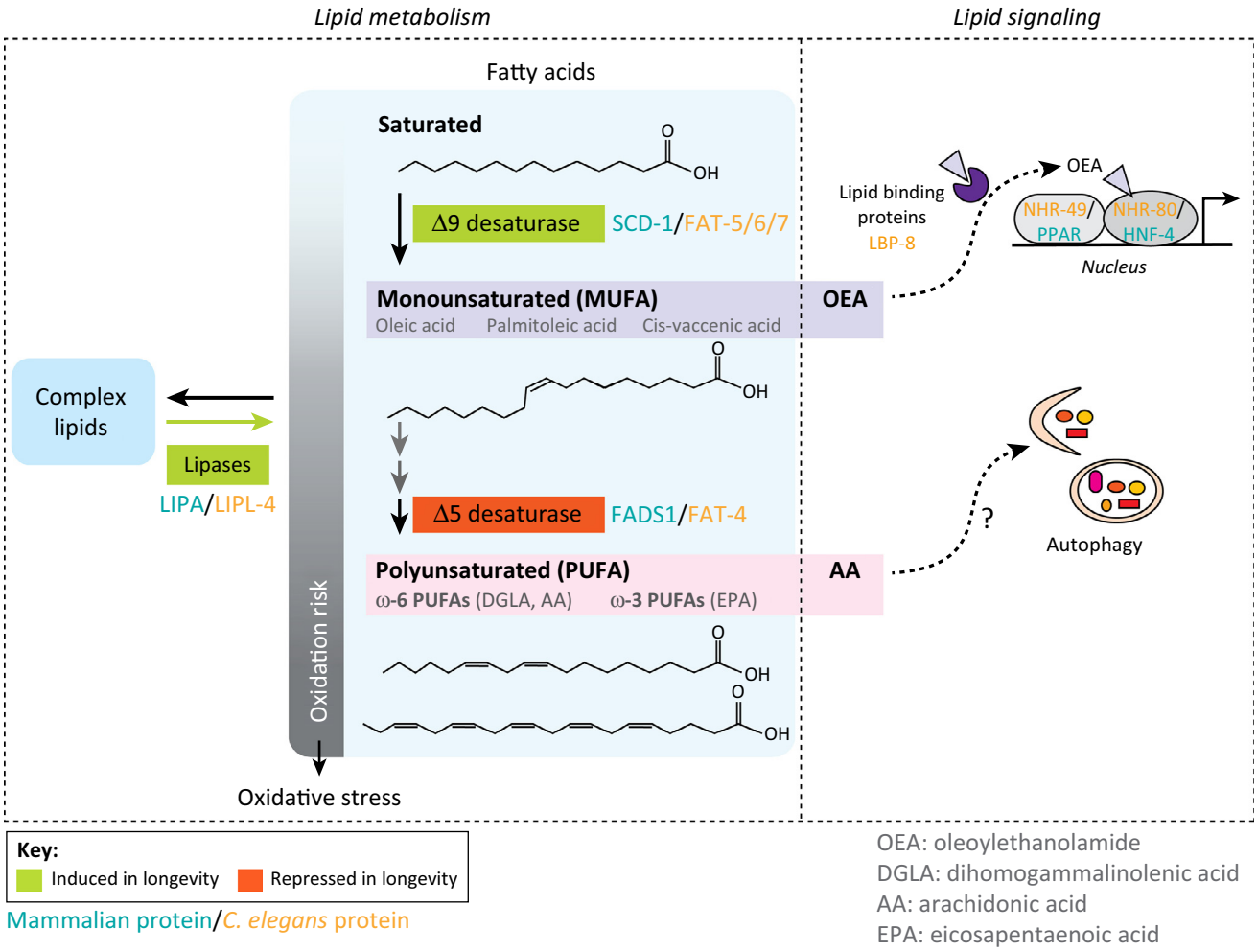

Figure 1. Lipid Metabolic Pathways, Profiles, and Signals Implicated in Longevity. Free fatty acid (FA) chains can be liberated from complex fats by the activities of lipases. Several lipases are elevated under conditions that extend lifespan in *Caenorhabditis elegans*, including LIPL-4. FAs can be saturated (no double bonds), monounsaturated (MUFAs; one carbon–carbon double bond) or polyunsaturated (PUFAs; two or more carbon–carbon double bonds). Increasing desaturation can make FAs more susceptible to oxidation by free radicals. In *C. elegans*, elevation of Δ9 desaturases (FAT-5/6/7), which produce MUFAs, is associated with longevity under several conditions. Conversely, Δ5 desaturase, which can produce highly polyunsaturated FA chains, is reduced in long-lived worms. FA desaturases produce many other MUFAs and PUFAs that are present in biological samples. Exploring how these lipid molecules determine longevity would be of great interest. FAs and other lipids can also act as signaling molecules to influence lifespan. Oleoylethanolamide (OEA), which is elevated in response to increased LIPL-4 expression in worms, activates key metabolic transcriptional regulators to extend lifespan. Lipid-binding proteins mediate OEA signaling and may be important for other lifespan-extending lipid signals within cells or across tissues. ω-6 PUFAs, also elevated by increased LIPL-4 expression, can induce autophagy through unknown mechanisms.

longevity in worms and mammals, especially in the context of long-lived mutants that are known to exhibit numerous other cellular effects.

Although these findings imply that reducing PUFAs delays aging, increasing specific PUFAs may also promote lifespan extension. In *C. elegans* and cell lines, supplementation with ω-6 PUFAs activates autophagy, a prolongevity process that promotes survival under nutrient deprivation [7,8]. In worms, increased expression of lipases, which can liberate FAs from complex lipid molecules, promotes high levels of ω-6 PUFAs [8] but also of many other FAs [9]. Both induction of lipases, particularly LIPL-4 (homologous to mammalian LIPA), and increased autophagy are required for longevity in worms lacking a germline [3]. Lipases also support autophagy induction during starvation [8], raising the possibility that lipases and the free FAs they generate are important for longevity in dietary restriction. Additional genetic experiments in nematodes and mammalian cellular and organismal models, combined with lipidomics to identify relevant products of lipid metabolic enzymes such as lipases and desaturases, might shed light on the relative roles of MUFAs and PUFAs in longevity in different contexts. In addition, more work is needed to determine the effects of MUFA