Pitch Riekelt Houtkooper – complex lipids

Note: this pitch is based on a project I submitted as ERC CoG. Some details of the work are "anonymized" since the work is not published yet, but can be shared with people who are interested.

The challenge

Increased life expectancy in human populations comes with an increased rate of age-related diseases. This includes cardiovascular diseases, neurodegenerative diseases, chronic kidney disease, and metabolic diseases such as obesity and type 2 diabetes, as well as an increased susceptibility to a severe clinical outcome upon influenza or COVID-19 infection. Aging has long been considered a passive process that could not be reverted or slowed down. However, it is now clear that the aging process is actively regulated and can be influenced to reduce the burden of age-related diseases. This plasticity of the aging process opens the door for fundamental research to discover mechanisms that regulate aging, and for the development of therapeutics to promote healthy aging in humans.

The opportunity

For the past years, we have been interested in how lipids are involved in aging. Many associations have been made between lipid biology and disease, including acquired lipid disorders including atherosclerosis, as well as inherited metabolic diseases such as fatty acid oxidation deficiencies. These lipid disorders often implicate well-known "simple" classes of lipids such as cholesterol or fatty acids in their pathophysiology, and we now know that these lipids are also disturbed in aging. More recently, we have observed a shift towards research on **complex lipids**, which are defined as lipids with three or more chemical moieties (e.g. glycerol, fatty acids, and one phosphate group) and that have polar properties. Phospholipids are a prototypical representative of such complex lipids. They have long been considered passive bystanders simply constituting biological membranes, also because no analytical techniques were available to get full insight in their complexity. This has changed 180 degrees, in part due to implementation of new analytical technologies. Lipidomics involves the comprehensive analysis of lipid species through mass spectrometry. In our group, we are able to detect, annotate and quantify >1500 unique lipid species using ultra-high performance liquid chromatography (UPLC)-high resolution mass spectrometry (HRMS). Studies in invertebrate and mammalian models suggest that phospholipids play a role in the regulation of age-related disease and longevity. However, **identification of universally conserved lipid changes that occur during aging and age-related diseases is lacking, and whether these specific lipids may be directly driving the aging process is unclear**.

The offer

We used our lipidomics platforms to map this uncharted territory. My team compared the lipidome in ten different tissues from young (3 month) versus aged (2 years) mice, which revealed a drastic accumulation of a specific complex lipid class occurring in all tissues (unpublished). Interestingly, this lipid not only accumulates in aged mice; it also (1) accumulated in urine from individuals with metabolic syndrome and chronic kidney disease; (2) accumulated in muscle biopsies from older adults (collaboration Patrick Schrauwen); (3) is lowered in muscle biopsies from individuals undergoing exercise, a healthy aging intervention (collaboration Patrick Schrauwen). Moreover, we found that the main gene involved in the lipid's synthesis increased in expression during in vitro and in vivo kidney aging. Remarkably, knockdown of the worm ortholog of this gene increased lifespan of *C. elegans* by 20%, suggesting causality. Though these results are very promising, many questions remain with respect to the actual molecular mechanisms and the extent of this lipid being an aging lipid. For instance, (1) does the lipid or associated gene change in abundance upon senescence or senescence reversal?; (2) does the lipid/gene changes in tissues of individuals with age-related diseases? We would very much welcome suggestions and access to materials to answer these questions in collaboration.