



Commentary

Lipidomics and the quest for brainy lipids

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The brain, our most complex and inaccessible organ, is mostly made of lipids. In fact, more than 60% of its dried weight consists of lipids or fats covering a broad number of chemical structures [1]. Lipids perform many critical structural and signalling functions but, since we do not know the full composition of the brain, we are not sure how its lipids make-up may change over time [2]. One might think that lipids decrease in the brain with aging, we know through imaging that brain volume decreases with age in the healthy and more dramatically in persons with Alzheimer's Disease [3].

Considering the above, could cognition decline be associated with lipids in the brain, perhaps also affecting the lipid composition in the blood? The latter is the question posed by Lefevre-Arbogast et al. in "Early signature in the blood lipidome associated with subsequent cognitive decline in the elderly: a case-control analysis nested within the Three-City cohort study", in this issue of *EBioMedicine* [4]. The team studied the lipid composition in the sera of a group of more than 700 healthy individuals whose cognition decline was measured over 12 years.

The study has an interesting design because the cohorts span three cities in France. Once they matched the participants, the first cohort was in the few hundreds, with balanced numbers in gender, age and education. The team decided to look first at a group of 400 volunteers, calling this their discovery cohort, and the results were then compared with participants in another city. By testing the reproducibility of results in the second cohort, lipids that matched were selected as the main results.

Discovery and validation is a pipeline that is very useful for -omics studies because the number of variables are huge versus the number of questions that we ask the data and it can be easy to over fit the data. In this study, the main outcome is cognition deterioration and the two cohorts were found to have 6 common lipids from 5 different lipid families. The team's hypothesis is that in older healthy people these lipids in blood can give information on biological mechanisms and the chance of declining cognition in the following ten years,

hence they can be a target for prevention of cognition decline. The lipids selected are known to have functions in membrane fluidity, myelination and lipid rafts, functions that lipids perform in the brain.

Lipidomics is the method used here and is one of the newer -omics, so it might be also new for some readers of *EBioMedicine*. In a nutshell, it is the analyses of a large number of lipids, for example in blood, where we can find thousands of small molecules of which most are lipids. Some of these single-lipids will be transported in HDL or LDL particles and other size particles or will be in free form. In this work, 189 single-lipids in serum were measured.

Because lipidomics in blood detects many lipids and the technology is not widespread, the challenge is to understand their various functions. In fact, in the past, lipids have been thought of as mere structural molecules but their bioactivity is now a hot topic [5]. For example, some lipids are well known, such as the cholesterol derivatives cortisol, testosterone and progesterone. Other lipids are totally different in structure; who has not felt the heat when eating capsaicin?, this is the lipid that makes chillies spicy and surprisingly, it is also an anti-inflammatory. In my laboratory, we have long been studying lipids in Alzheimer's and found lipids with sedative effects that could be released in the case of amyloid accumulation in the brain [6].

Lipidomics as a science is based on another science, mass spectrometry. There are many labs working on advancing both fields and almost every single lab, including mine or the company employed in this study, measure the main lipid families and to a different degree of certainty the chemical structure of single lipids. The measurement can be chosen to be qualitative, more or less exact, semi-quantitative, or quantitative, the latter being the best possible measurement. In this paper the authors study 170 different lipids, which is a huge number compared with the clinical standard lipid measures. The take home message for lipidomics is that it is NOT one method but rather a process that means detecting an extraordinary number of lipids within a lab-chosen quality standard.

The lipidomics field is moving into combining with other -omics to be able to acquire what is called a systems medicine approach to disease. The idea behind omics integration is that all those single molecules in unison are the perpetrators of the disease's phenotype. That is where the current machine learning algorithms, like the LASSO regression used in the study, help in making sense of the complex relationships between molecules.

To wrap up, the paper by Lefevre-Arbogast et al. is very exciting and has the potential of being tested further in a clinical trial. As we know, lipids can be modulated with diet, dietary supplements, drugs

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and natural products. Some nutritional beverages based on lipids have seen positive results in clinical trials for cognition [7]. Omegas fatty acids, ketones, olive oil, berries, ginseng or other natural products have seen beneficial cognitive results in the past, but the evidence is mixed and many questions remain as causal molecular links to cognition have not been proven. Our previous work showed that bigger lipids that incorporate omega fatty acids in their structures were depleted with cognitive decline, our next task is to study if this is causal or a symptom [8].

The field is quickly evolving so watch out for the next discoveries in lipid mechanisms in cognition. The toolbox has gone from having a handful of lipids, HDL, LDL, TAGs, fatty acids, omegas and cholesterol, to having two thousand or more so imagine how much there is to discover about lipids and the brain.

Declaration of Competing Interest

The author declares no conflicts of interest

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