Nutrilipidomics: A Tool for Personalized Health

Chryssostomos Chatgilialoglu* and Carla Ferreri*

ISOF, Consiglio Nazionale delle Ricerche, Via Piero Gobetti 101, 40129 Bologna, Italy

Keywords: Membrane lipidomics; Lipidomic profiles; Fatty acids; Nutrition; Biomarker; Nutraceuticals

“Omics” technologies have an important role in the comprehension of metabolism and signaling pathways at a molecular level, aiming at envisaging early stages of malfunctioning and disease onsets, as well as contributing to the advancement of molecular diagnostics and biomarkers for health care and disease prevention [1]. The “omics” approach gives also new hopes to the disease prevention and treatment. It is worth underlining that the development from “bench-side” to “bed-side” and to commercial health products must occur in a way that any effect should be prematurely promised to consumers [2].

“Omics” monitor molecular levels and activities of genes, proteins, carbohydrates, lipids and all their metabolites, offering a systematic view of the most relevant biological pathways and responses. This includes effects of nutritional elements. On this basis, it is timely to develop medical approaches where the “molecular” status of the patient is evaluated during the anamnesis, coupled with clinical observation and set-up of a personalized therapeutic strategy, including dietary intervention. Genomics in the nutritional area created the field of nutrigenomics dealing with the effects of nutritional elements on gene expression and transcription factors, however the number of studies is still considered limited to allow for a full application to medical care [3].

On the other hand, lipidomic profiling is an important tool to probe the impact of nutrition and metabolism [4], being fatty acid-containing molecules one of the most important lipidomic targets. This subject connects technological and analytical advancements of the last decade to decades of biochemical and nutritional research on fatty acids (FAs), highlighting their important roles for the membrane phospholipid structures and functions, the regulatory and signaling networks, the activation of specific receptors, the influence on expression of genes and protein responses.

Moreover, a full scenario of the type and quantity of FAs coming from the interplay of biosynthesis and diet is also available. The essentiality of omega-6 and omega-3 polyunsaturated fatty acids (PUFA) for eukaryotic cells (i.e., linoleic acid and α-linolenic acid) and the role of specific lipid enzymes, namely desaturases and elongases, have been thoroughly studied. The essentiality of FAs has been recognized in medicine (e.g. dermatology, ophthalmology, and cardiology) and fascinating involvements of FA pathways have been discovered for various pathologies (e.g. cancer, obesity, diabetes, and neurodegeneration) [5]. Also the market developed, since the inputs of these biological and medical research generated an exponential growth of formulations containing FAs and related cofactors, which are used as nutraceuticals or dietary supplements. In Europe, following the Regulation 1924/2006, the European Food Safety Agency (EFSA) has started to revise scientific basis for health claims of nutritional supplements, and the effects of FAs have been obviously included in the survey. A few health claims have been accepted so far, creating concerns in the criteria used to assess the effects and in the future directions of supplement design and production.

FA-based lipidomics in the nutritional area is ready for use. We coined the term “nutrilipidomics” for an innovative tool for personalized health care [6]. In this case, a specific lipid pool belonging to the cell membrane compartment of a specific tissue is the target, i.e., the FA composition of membrane phospholipids as a comprehensive indicator of metabolic and nutritional effects. The drawing in Figure 1 shows the context of nutrilipidomics having the FA content of cell membranes at the crossroad of various contributions.

The membrane FA asset, i.e., saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA), present in the phospholipids is characteristic of each tissue. A natural adaptation response is active and the appropriate changes of the FA microenvironment ensure the best functioning of membrane proteins, receptors, pumps and signals in tissues, according to environmental and metabolic needs. Therefore, FA status is dynamic including the remodeling that follows the propagation of stimuli, where FAs are continuously released from membranes to act as mediators and specific ligands. It is worth mentioning that FAs as inducers of metabolic cascades and gene expression are studied in the field of nutrigenomics, whereas the lipidomic monitoring should also be required [7,8]. Membrane composition is also related to an homeostatic control that keeps constant the working environment of...
protein, channels and receptors by a meticulous FA balance, involving 
hydrolyase, esterase and transferase enzymes. A seminal example is 
provided by arachidonic acid as fundamental PUFA constituent of 
membranes, and also element released from membranes to become 
precursor of eicosanoid mediators and receptor ligands [9]. Moreover, 
membrane FAs come into play during cell replication, since the new 
cells need them and the fatty acid composition has to fulfill the best 
tissue performance. As matter of facts, it is not yet clear whether the lack of 
an efficient membrane FA composition can be somehow checked 
at any stage of cell and tissue development, perhaps in combination 
with the known extrinsic apoptotic pathways derived from membrane 
signaling. Membrane lipidomics can provide a snapshot of the 
membrane composition as a multifactorial result. This snapshot can 
evidence failures of the FA availability and, exploiting the efficiency of 
the natural lipid remodeling and the cell turnover, suggest a targeted 
re-equilibrium strategy for restoring this functional pool. Membrane 
lipidomics is the basic tool of the nutrilipidomic approach to target 
personal needs and use the full benefits of a nutrition-based strategy. 
The choice of the cell for nutrilipidomics is based on the presence of 
all representative fatty acid families and the reasonable cell lifetime 
for evaluating the turnover and the acquired balance, together with 
the influence of correction factors. As shown in Table 1 from the cell life 
spans, erythrocyte membranes emerged as a valuable choice.

In erythrocyte membranes a meaningful cohort of FAs can provide 
the basic data set [6]. This panel also includes FA ratios and enzymatic 
indexes, calculated by the relative ratios among fatty acid families and 
substrates: the ratio SFA/MUFA can indicate biosynthetic and dietary 
contribution, which create the balance between these two FA families 
in the membrane compartment, regulating structural organization, 
biophysical properties and functioning. From changes at molecular 
level most of the harmful consequences of SFA for health can indeed 
arise [10]. In this respect the role of unsaturations, namely the natural 
double bond content, is extremely important for favorable membrane 
biophysical properties of fluidity and permeability, as well as for 
biochemical functions and signaling cascades. It is worth underlining 
that the unsaturated content is correlated to the functioning of 
enzymes, namely Δ5-, Δ6- and Δ9-desaturases. These enzymes work 
regio- and stereo-specifically, meaning that the position and geometry 
of the double bonds are fixed and have defined biological meanings. 
Obviously, the dietary supply of MUFA and (PUFA) residues regulates 
these enzymatic activities, and a critical interpretation of the individual 
status can be carried out combining with complete anamnesis and 
dietary habits of the subject. Evaluation of desaturase genes can be 
used as risk factors for several diseases [12,13].

The effects of FAs as essential elements for health generated a 
tremendous increase of commercial products containing plant and 
animal oils as mentioned above. The use of these supplements can 
occur without medical prescription and a strong advertisement 
campaign on the nutraceutical effects for skin, muscle, liver, brain, 
heart, joints health, together with slowing aging, rendered them the 
products of choice by millions of consumers, considering them as 
natural, therefore safe, substances.

Nutrilipidomics can have an important role in rendering this 
choice personalized and adequate to personal needs, being evident the 
strict relationship between the status verified by membrane lipidomics 
and the type and dosage to be used. Indeed, it must be considered that 
hydrophobic substances like FAs accumulate especially following high 
dosages for long periods. This can certainly influence the FA pools with 
modifications also of the membrane content. Such changes should 
not be random but strategically used for improving the individual 
condition. Another related aspect is the reactivity of unsaturated FAs with free radicals, which can occur by two main processes: 
peroxidation and isomerization. Oxidized and trans-FA are a large 
variety of molecules with many biological effects, but their excess has 
been recognized to be harmful for health [14]. Research have already 
evidenced that lipid peroxidation can be indeed connected with the use 
of PUFA supplementation [15].

Why are lipidomics and nutrilipidomics still awaiting the clinical 
use? As a partial explanation some limiting factors could be individuated, 
such as the time-consuming protocol for membrane isolation and the 
difficulty to couple molecular and clinical evaluation in the absence 
of a specific formation during the academic courses. Obstacles can be 
removed also in view of amelioration of high-throughput devices and 
modernization of the university programs.

What are the perspectives of FA analysis and nutrilipidomic 
approach? Firstly, they can be used as effective preventive tool for 
health care based on nutritional and nutraceutical elements. It must 
be underlined that the membrane unbalance can occur in the absence 
of a pathological status, therefore be silently influencing the molecular 
status much before the clinical status. Secondly, nutrilipidomics can 
be a useful tool to modernize the dietary software, introducing the 
concept of fat intakes not only as calories (25-35% of the energies), but 
but differentiating and calculating the type and quantity of different FA 
sources needed for the individual status.

With the nutrilipidomics approach FAs will be fully employed as 
nutraceuticals. Indeed these substance satisfy the three basic requisites 
for nutraceuticals: (i) they are needed for humans, their intake is also 
from external sources, that is a must for essential fatty acids; (ii) possible 
scarce intake or consumption by known modes can lead to impairment 
of their levels in the body and, consequently, of most tissues and 
metabolic pathways; (iii) their supplementation can ensure health of 
tissues and functions. However, to be considered nutritional elements 
with pharmaceutical (health) effects, i.e., nutraceuticals, they must 
have a precise site of action and a specific type and dosage for efficacy. 
Indeed, protocols reporting the FA supplementation have never been 
run by considering personalized treatments or dosages, neither upon 
verification of the oxidative and metabolic conditions, as well as their 
starting FA profile. This methodological issue can probably explain the 
variability and contradictions of the effects described in the literature, 
which created also doubts in the effectiveness of the "lipid therapy". In 
the approach of nutrilipidomics, the use of erythrocyte membranes to 
evaluate the subject’s status and the type of personalized intervention 
create the evidence-based choice of supplementation and the dosage 
tailored on the subject’s conditions.

Another element of the nutrilipidomics approach is to bring 
innovation for the nutraceutical design. Databases of membrane 
lipidomic analyses can be organized in order to individuate profiles

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Lifespan</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell</td>
<td>Hours- 2 days</td>
</tr>
<tr>
<td>Intestinal cell</td>
<td>7 days</td>
</tr>
<tr>
<td>Epidermis cell</td>
<td>18-20 days</td>
</tr>
<tr>
<td>Red blood cell</td>
<td>120 days</td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>150 days</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>6-15 months</td>
</tr>
</tbody>
</table>

Table 1: Mean Lifespan of Different Cell Types.
of subjects having different health conditions. The multivariate analysis for lipidomics profiles can be also implemented with parameters derived from other “-omics” and molecular diagnostics. In this way, nutrilipidomics can motivate an innovative productive chain for nutraceutical lines customized on the basis of the “-omics” profiles, offering its scientific support to the identification of effective formulations and dosage in nutraceuticals.

This approach can be very useful for societal needs and consumers: the need of a market of nutraceuticals proposing products based on real needs, thus becoming closer to consumers, and the timely establishment of health care operators able to couple the patient’s clinical conditions with the corresponding molecular profile as a rationale for personalized intervention including nutritional elements. Overall, nutrilipidomics is expected to boost personalized health with an ideal balance between scientific evidences and market sustainability.

References