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Nutrilipidomics: A Tool for Personalized Health

Chryssostomos Chatgilialoglu* and Carla Ferreri*

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

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"-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 explore 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

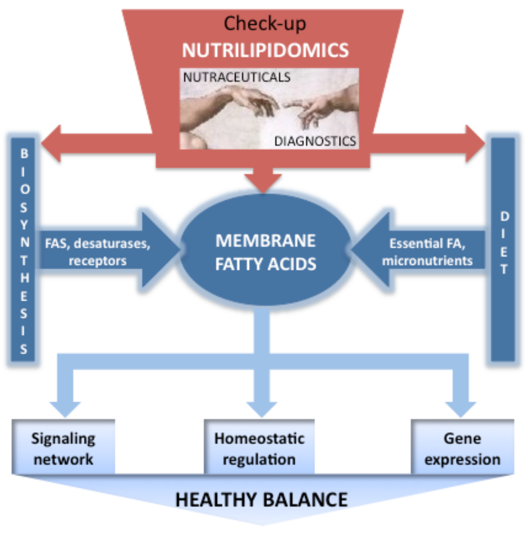

Figure 1

***Corresponding authors:** Chryssostomos Chatgilialoglu, ISOF, Consiglio Nazionale delle Ricerche, Via Piero Gobetti 101, 40129 Bologna, Italy, Tel: +390516398309; Fax: +390516398349; E-mail: chrys@isof.cnr.it

Carla Ferreri, ISOF, Consiglio Nazionale delle Ricerche, Via Piero Gobetti 101, 40129 Bologna, Italy, Tel: +390516398289; Fax: +390516398349; E-mail: carla.ferreri@isof.cnr.it

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protein, channels and receptors by a meticulous FA balance, involving hydrolase, 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 effected by genomics [11] and in parallel by enzymatic indexes in the lipidomics of erythrocyte membranes. Nowadays these parameters are 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.

Cell type	Lifespan
White blood cell	Hours- 2 days
Intestinal cell	7 days
Epidermis cell	18-20 days
Red blood cell	120 days
Hepatocyte	150 days
Adipocyte	6-15 months

Table 1: Mean Lifespan of Different Cell Types.

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 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 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.

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