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Review

Systems biology strategies to study lipidomes in health and disease

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ABSTRACT

Lipids are a diverse group of metabolites that have many key biological functions, acting as structural components of cell membranes, energy storage sources and intermediates in signaling pathways. Due to their importance lipids are under tight homeostatic control and exhibit spatial and dynamic complexity at multiple levels. It is thus not surprising that altered lipid metabolism plays important roles in the pathogenesis of most of the common diseases. Lipidomics emerged as a discipline which is dedicated to global study of lipidomes, including pathways and networks of lipids in biological systems. When studying the lipidomes at a systems level, one of the key challenges is how to address the lipid functionality at many physiological levels, from metabolic and signaling pathways to spatial systems such as cellular membranes and lipoprotein particles. Besides the better analytical techniques to study lipids, computational techniques have started to emerge which enable modeling of lipidomes in their spatial and dynamic context. Together, the recent methodological advances in lipidomics have a potential to open novel avenues for predictive and preventive medicine. This review focuses on progress in systems approaches to study lipids in health and disease, with specific emphasis on clinical applications.

Contents

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1. Introduction

While the strong genetic component of many complex diseases is well documented, with heritability estimated *e.g.* at 40% or higher in the metabolic syndrome [1] or in the order of 65% or higher in schizophrenia [2], it is also clear that current approaches studying genetic associations with disease traits can explain only a fraction of the known disease heritability [3]. The systems biology view suggests that most of the genetic component of complex disease susceptibility is not to be found in individual genes, but in their interactions with other genes as well as with the environment [4].

Systems thinking in the life sciences is not new. The concepts such as 'metabolic control analysis' [5] and 'systems theory' [6] to describe the biological systems had been introduced already in 1970s, but their utilization in experimental biology has been limited due to the lack of quantitative data needed to parameterize the mathematical models. Biologists have instead resorted to a reductionist approach, focusing on elucidating the individual molecular components such as genes and their products by studying them in isolation. In such an experimental setting, dependencies between the molecular components and their specific functions were typically established by applying single-component interventions such as by gene knock-down experiments. The main limitation of such approach is that it does not account for global interconnectivity of the system and is thus strongly context-dependent [7]. This may in part explain recently documented poor reproducibility of conclusions from molecular biology studies [8]. Nevertheless, the reductionist approach has been essential for generating the biological knowledge including identifying components and structures of the molecular networks as we know today; and will remain as a component of hypothesis-driven scientific method which complements the systems approach.

The 'omics' revolution which started in the 1990s introduced many new tools for life science research. By applying the 'omics' approach, molecular snapshots of biological systems can be generated, allowing for the study of comprehensive molecular profiles in time as dependent on genetic or environmental variation. However, here also lies a conceptual challenge. Since the high-dimensional 'omics' data usually reflects the changes in the complex multi-level network of the underlying components, one cannot only adopt the still pervasive traditional reductionist experimental paradigm to model and interpret it. Not surprisingly, such an approach has led to many disappointments. Joyner and Pedersen for example remarked in a recent commentary that "*. . .fundamentally narrow and reductionist perspective about the contribution of genes and genetic variants to disease is a key reason 'omics' has failed to deliver the anticipated breakthroughs*" and point out "*the critical utility of key concepts from physiology like homeostasis, regulated systems and redundancy as major intellectual tools to understand how whole animals adapt to the real world*" [9]. Systems biology approach is therefore essential in order to deal with the 'omics' data; thus shifting the research emphasis from single molecular components to how they together contribute as parts of a complex network to a specific phenotype or biological function [10–13].

Data integration with mathematical models is a key component of systems biology, aiming to model the data in the context of the system of interest. Both experimental and modeling approaches in systems biology may vary, depending on the system (Table 1). For example, at the cellular level, the systems approach may involve global modeling of cellular networks (*e.g.*, metabolic networks), based on several levels of the data (*e.g.*, fluxomics, metabolomics, proteomics, genomics). In the clinical setting, the systems approach may involve identification of molecular profiles associated with progression of the disease, as well as applying modeling to help identify the putative underlying biological mechanisms or principles. While still being a far-reaching goal at present, ultimately the aim of systems approaches to study health and disease is also to link the models across different levels, from clinical to cellular.

In the context of human health and disease, the measurement and characterization of traits that are modulated but not encoded by genotype, referred to as intermediate phenotypes, is of particular interest and a key component of the systems approach [29–31]. Concentrations of specific groups of metabolites including lipids are sensitive to genetic variation [32–34], diet [35], development [36], age [37], immune system status [20,38], and gut microbiota [39–42]. Metabolome is also highly dynamic [43], *i.e.*, metabolite levels are sensitive to specific challenges including physical exercise [44], oral glucose tolerance test [45], fasting [43], as well as to circadian rhythms [46]. Distinct pathophysiologically relevant features of metabolome may reveal themselves only when the organism is put under the specific challenge [43]. Metabolomics, a global study of metabolites and their pathways, has emerged as a powerful approach for the characterization of complex phenotypes and biomarker discovery [47–49]; which also makes metabolomics a powerful platform for personalized medicine [50].

2. Role of lipidomics in systems biology

Lipidomics emerged as a discipline closely related to metabolomics and is dedicated to the global study of lipidomes, including pathways and networks of lipids in biological systems [51–55]. From the systems biology perspective, the study of lipids presents several challenges as well as opportunities. Lipids are highly diverse [55,56] and exhibit spatial and dynamic complexity at multiple levels [57,58]. For example, lipids constitute ~50% of the mass of most animal cell membranes and exhibit a high degree of specialization in specific cellular compartments. The relevant temporal scales of lipid metabolism also vary widely, *e.g.*, from dynamics of lipid membranes at the nanosecond/microsecond scale, to lipoprotein metabolism at the minute/hour scale, to systemic rearrangements of lipid metabolism with age. The organisms have built-in robust mechanisms which help to maintain the lipid homeostasis under the varying environmental challenges [59].

For example, cellular lipid homeostasis is regulated by a family of membrane-bound transcription factors designated sterol regulatory element–binding proteins (SREBPs). SREBP1c regulates the genes of membrane glycerophospholipid metabolism, while SREBP2 preferentially activates the genes of cholesterol metabolism. Silencing of SREBP1c *in vivo* surprisingly did not lead to disruption of phospholipid metabolism [60]. The loss of SREBP1c function was instead compensated by overexpression of SREBP2, which in turn also led to accumulation of cholesterol. This is a good example of 'allostatic adaptation' aimed at induction of short-term corrective changes to regulatory systems [61]. However, if such an adaptive response remains activated for too long, the maintenance of metabolic homeostasis might come at a metabolic cost, or 'collateral damage', defined by McEwen as allostatic load [62] (*e.g.*, the accumulation of cholesterol due to the adaptive activation of SREBP2).

Development of a complex disorder, from early prodromal phases when the first non-specific disease symptoms occur to overt disease, is usually a long process which proceeds through several phases where allostatic adaptations play a crucial role [48,59] (Fig. 1). Given such a tight homeostatic regulation of lipid metabolism, the study of lipidomes in different stages of health and disease may not only provide a direct readout of activated lipid-related pathways, but may also help to unravel the 'allostatic forces' behind the maintenance of physiological balance as well as