

Chapter XXI

Systems Biology Strategies in Studies of Energy Homeostasis *In Vivo*

Matej Orešič

VTT Technical Research Centre of Finland, Finland

Antonio Vidal-Puig

Institute of Metabolic Science, Addenbrooke's Hospital, UK

ABSTRACT

In this chapter the authors report on their experience with the analysis and modeling of data obtained from studies of animal models related to obesity and metabolic syndrome. The complex interactions of genetic and environmental factors contributing to the failure of energy balance that lead to obesity, as well as tight systemic regulation to maintain energy homeostasis, require application of the systems biology strategy at the physiological level. In vivo systems offer the possibility of investigating not only the effects of specific genetic modifications or treatments in selected tissues and organs, but also to elucidate compensatory allostatic mechanisms induced to maintain the homeostasis of the whole system. A key challenge for systems biology is to characterize different systems' responses in the context of activated pathways. One possible strategy is based on reconstruction of tissue specific pathways using lipidomics, or metabolomics in general, in combination with proteomic and transcriptomic profiles. This approach was applied to obese mouse model and revealed activation of multiple liver pathways that may lead to metabolic products, which may impair insulin sensitivity.

INTRODUCTION

The system controlling the energy balance is tightly regulated. The failure of mechanisms controlling the energy balance may lead to obesity. The causes of such failure may be genetic defects in the mechanisms

controlling food intake, energy expenditure, partition of nutrients towards specific organs, expandability of the adipose tissue, or genetically inherited traits leading to inactivity. The environmental factors interacting with genetically determined traits are clearly involved, as the obesity is a rather recent problem of the last few decades. The biological redundancy adds another layer of complexity. Since energy homeostasis is so central to survival, the system has evolved towards a tightly regulated redundant system characterised by: (1) similar responses induced by different pathways and (2) compensatory mechanisms systems aiming to restore the steady state of energy homeostasis.

Systems biology investigations aiming to address the complexity of obesity should therefore not only consider identification of mechanisms that may lead to obesity, but also aim to identify the compensatory biological strategies that are found *in vivo*. Some of these compensatory mechanisms may be targeted to increase the success rate of current strategies to lose weight. As obesity may lead to a number of complications such as diabetes and cardiovascular disease, a systems biology approach may be applied to identify early pathways that may lead to obesity-related complications, before they result in clinically identifiable specific diseases.

LIPIDOMICS

Lipids play an important role as structural components (*e.g.*, cell membranes), energy storage components (triglycerides in **adipose tissue**), and as signalling molecules (Vance & Vance, 2004). For example, changes in lipid function due to peroxidation, imbalanced fatty acid composition or their increased flux to peripheral tissues may contribute to development of disorders such as atherosclerosis, diabetes, metabolic syndrome or Alzheimer's disease (Watson, 2006; Wenk, 2005). Traditional clinical lipid measures quantify total amounts of triglycerides, cholesterol, or lipoproteins. However, serum lipid profile is much more complex at the molecular level. However, the modern **lipidomics** and **metabolomics** platforms enable quantitative characterization of 100s of diverse lipid molecular species across multiple lipid classes such as sphingolipids, phospholipids, sterol esters, and acylglycerols. In most cases, exact fatty acid composition for each detected lipid can be determined.

Lipid metabolism is regulated both by genetic and environmental factors. For example, using a unique monozygous twin study design in which young adult obese monozygous twins were compared with their non-obese co-twins, we have recently shown that that obesity already in its early stages and independent of genetic influences is associated with deleterious alterations in the lipid metabolism known to facilitate atherogenesis, inflammation and insulin resistance (Pietiläinen et al., 2007). The study also demonstrated the sensitivity of the metabolomics platforms since subtle pathophysiological changes were detected well prior to changes in commonly utilized clinical measures. Of special interest and clinical relevance was the finding that the atherogenic lipid profile of the obese co-twins was associated with whole body insulin resistance, something that could not be detected using classical lipid measures and inflammatory markers only.

IN VIVO STUDIES

Lipidomics is increasingly utilized in functional characterization of genetic or environmental interventions *in vivo*. *In vivo* systems offer the possibility of investigating not only the effects of specific genetic

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