

# Chapter 2

## Systems Biology in Human Health and Disease

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**Abstract** If we are to study complex multi-factorial disorders such as Metabolic Syndrome (MetS) by applying the state-of-the-art ‘omics’ technologies, the reductionist approach commonly applied in life sciences is no longer suitable. In order to understand the adaptive changes in molecular networks in different stages of the disease pathogenesis, a comprehensive view of the system is needed because activation of different pathways may still lead to the same functionality, but with different metabolic costs. Systems biology emerged as an inter-disciplinary field of study that focuses on complex interactions within and between biological systems, using a more holistic perspective approach to biological and biomedical research. While the importance of the systems approach has already been recognized decades ago, the experimental and modeling techniques have matured to the level where comprehensive characterization of biological systems at the molecular level is now feasible.

**Keywords** Allostasis · Allostatic load · Bioinformatics · Genomics · Gut microbiota · Lipid metabolism · Metabolic networks · Metabolomics · Proteomics · Systems biology

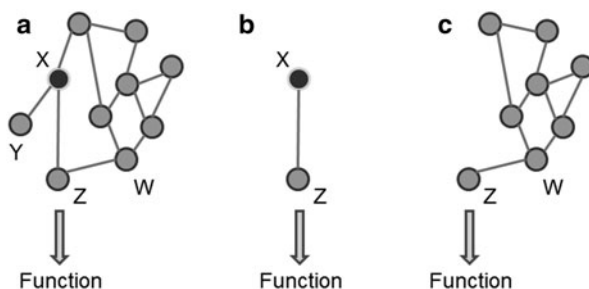
### 2.1 Need for Systems Approach to Study Health and Disease

Molecular biology contributed many essential experimental tools used in today’s life science research. However, its early days also introduced the still pervasive reductionist approach to study the biological systems. While the concepts such as ‘metabolic control analysis’ (Kacser and Burns 1973) and ‘systems theory’ (von Bertalanffy 1969) to describe the biological systems had been introduced already in 1970s, their practical utilization was limited due to the lack of quantitative experimental data needed to parameterize the mathematical models. Instead, molecular biologists resorted to a simpler experimental paradigm, focusing on the elucidation of function of single molecular components such as genes and their products by studying them in isolation. In such setting, dependencies of specific biological functions on specific

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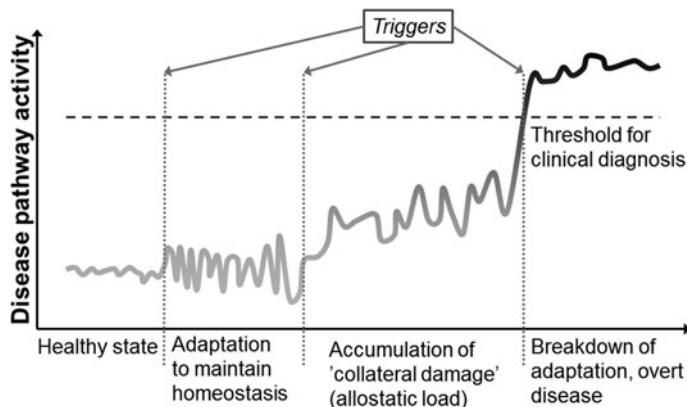
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**Fig. 2.1** Limitations of the reductionist approach when studying complex interconnected systems. **a** Real biological network, showing nodes as molecular entities and edges as their interdependencies. **b** Focus on single component only, X, will by experimentally modulating X lead to conclusion that X controls functionality of Z. **c** Potential other networks that may regulate Z as well as modulate function of X are disregarded by the reductionist approach

molecular components are usually sought, e.g., as established by single-component interventions such as by gene knock-down experiments. Following a series of well thought-through experiments of that kind, a ‘mechanistic insight’ can be gained; which in the field of molecular biology means that in a specific context a specific component such as a gene controls a specific biological function.

The fundamental limitation of the reductionist approach as applied to molecular biology has been highlighted in an entertaining essay ‘Can a biologist fix a radio? Or, what I learned while studying apoptosis’ (Lazebnik 2002), where the author also remarked that “*an approach that is inefficient in analyzing a simple system is unlikely to be more useful if the system is more complex*”. Particularly, the experimental paradigm used in molecular biology does not account for global interconnectivity of the system and is thus strongly context dependent. As a simplistic but illustrative example, Fig. 2.1a shows a molecular network, where the nodes denote the interacting molecular components (genes, proteins, metabolites), while edges show their interdependencies (e.g., *via* molecular interactions or biochemical reactions). The investigation is focusing on the elucidation of the regulation of the molecule Z, which is associated with a specific biological function. The hypothesis being investigated is that Z is controlled by the molecule X. In order to test the hypothesis, function of X is modulated (e.g., by knock-down), which following the experiment leads to the conclusion that indeed function of Z depends on X (Fig. 2.1b). However, such an approach disregards potential other networks that may regulate Z as well as modulate the function of X (Fig. 2.1c). The so-obtained ‘mechanistic models’ therefore primarily describe the binary dependencies of molecular components and their functions. Given these binary relationships are usually acquired in different experimental contexts, i.e., the ‘other networks’ cannot be controlled for, it is thus not surprising that reproducibility of conclusions from molecular biology experiments is strikingly poor (Begley and Ellis 2012). Perhaps most troublingly, putting these ‘mechanistic models’ into practical use is very challenging because the global systemic context is lacking, i.e., it is difficult to know under what circumstances a particular binary dependency really holds.



**Fig. 2.2** Progression to complex disease, conceptualized by a single imaginary variable denoted as ‘disease pathway activity’. Adaptation and its metabolic cost play a key role in this process

While the discussion above mainly referred to the studies at the levels of cells, the challenges are even bigger when attempting to apply the reductionist approach at the whole-organism physiological level (Joyner and Pedersen 2011). In such setting, the system’s components and their interactions occur at many levels and timescales, from individual molecules to tissues and organs. The organisms have built-in robust mechanisms which help to maintain the essential physiological functions such as metabolism under the varying environmental challenges. When considering the experimental paradigm to address specific hypothesis at the whole-organism level, the familiarity with the physiological concepts such as homeostasis, allostasis, adaptation, robustness and resilience is thus essential. For example, maintenance of lipid composition of the cell membranes is essential for cell functionality and survival. Cellular lipid homeostasis is regulated by a family of membrane-bound transcription factors designated sterol regulatory element-binding proteins (SREBPs) (Horton et al. 2002). While SREBP1c regulates the genes of membrane phospholipid metabolism, SREBP2 preferentially activates the genes of cholesterol metabolism. Surprisingly, knock-down of SREBP1c *in vivo* does not lead to disruption of phospholipid metabolism, which is because the loss of SREBP1c function is compensated by overexpression of SREBP2. However, as a cost of such adaption, mice lacking SREBP1c tend to accumulate more cholesterol (Horton et al. 2002). This is a good example of allostatic adaptation (the concept introduced in Chap. 1) aimed at induction of short-term corrective changes to regulatory systems. However, when such an adaptive response remains activated for long periods of time, the maintenance of metabolic homeostasis might actually come at a metabolic cost, or ‘collateral damage’, defined by McEwen as allostatic load (Korte et al. 2005). In the case of SREBP1c knock-down, the allostatic load is for example the accumulation of cholesterol due to the adaptive activation of SREBP2.

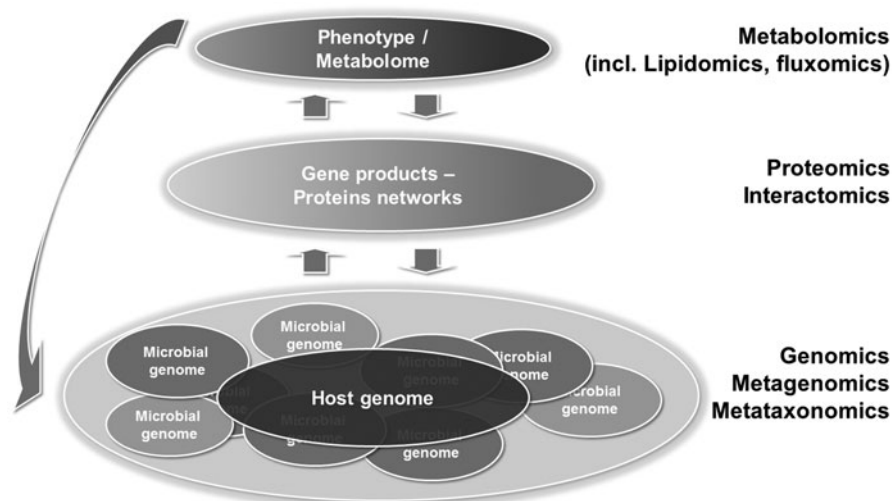
Development of a complex disorder, from early prodromal phases to clinically manifest disease, is usually a complex process which proceeds in several phases in which allostatic adaptations play an important role (Fig. 2.2, see also Chap. 1).

Environmental triggers such as change in lifestyle may impose a pressure on the organism to adapt (e.g., by changes in the underlying molecular networks) in order to maintain the system homeostasis. In the case of Metabolic Syndrome (MetS), this early phase corresponds to metabolically compensated obesity (or ‘healthy obesity’). However, extended duration of the activated allostatic response eventually leads to the accumulation of allostatic load, e.g., progressively losing the ability to store lipids in obesity. In this phase also the disease vulnerability increases, i.e., the organism is more sensitive to any triggers which may cause the disease, because it is reaching the limit of adaptability. At a certain point, this limit is reached and the organism is no longer able to adapt, leading to the overt disease (Fig. 2.2). The timelines of this progression vary between the individuals and also depend on the genetic make-up and the environment, including individual’s gut microbiota (Chap. 9). For example, some individuals can become very obese but still remain metabolically compensated while others soon develop metabolic co-morbidities of obesity such as type 2 diabetes (Virtue and Vidal-Puig 2008). Since the allostatic load accumulates over time, the earlier the stage of the progression to the disease, more likely the trend can be reversed. For this reason, it is important to detect the disease early in the process, prior to the appearance of clinical symptoms.

If we are to study diseases using the dynamic and physiological framework as described above, the reductionist approach is no longer viable. In order to understand the adaptive changes in molecular networks in different stages of the disease pathogenesis, a comprehensive view of the system is needed because different pathways may still lead to the same functionality, but with different allostatic load. Systems biology emerged as an inter-disciplinary field of study that focuses on complex interactions within and between biological systems, using a more holistic perspective approach to biological and biomedical research. While the importance of systems approach has already been recognized decades ago (Kacser and Burns 1973; von Bertalanffy 1969), the experimental techniques have also matured to the level where comprehensive characterization of biological systems at the molecular level is possible.

## **2.2 Key Enabling Technologies and Modeling Approaches of Systems Biology to Study Health and Disease**

The ‘omics’ revolution empowered us with the tools for comprehensive characterization of biological systems. For example, genomics, proteomics and metabolomics each cover a specific layer of biological organization (Fig. 2.3). At the genome level, in addition to host genome one must also consider the microbial genomes which together carry about 150-times as many genes as the host genome, primarily in the gut (Chap. 9). Gut microbiota is sensitive to environmental factors including the diet and can be considered as a ‘mediator’ between the environment and host biology. Gene products such as proteins regulate many biological processes in the cells including the biochemical networks involving metabolites. Small changes in enzyme concentrations and fluxes through their pathways may produce large changes in the



**Fig. 2.3** Factors influencing the metabolome and proteome and the key analytical platforms for systems biology to study health and disease. The metabolome is sensitive to genetic and environmental factors which may together contribute to the disease. Metabolomics is thus a powerful phenotyping platform in biomedical studies

concentrations of metabolites which are the end products of these pathways (Kell 2006). Gut microbes have distinct metabolomes and proteomes, which interact with the host as well as contribute to the regulation of the host metabolism (Tremaroli and Backhed 2012). In this context, the *in vitro* colon model described in Chap. 13 is a particularly valuable tool to study how the food metabolome is transformed by the gut microbes, thus providing physiologically relevant information about the food-derived metabolites entering the systemic host metabolism. In Part III, this book will introduce the key emerging technologies which support the studies of MetS using the systems biology approach, including in the context of nutrition. These include proteomics, metabolomics, fluxomics as well as the *in vitro* colon model.

In order to interpret the ‘omics’ data in the physiological context, models are needed which capture the relevant topology and dynamics of biological networks and processes under investigation. Global reconstruction of human metabolic network (Duarte et al. 2007; Thiele et al. 2013) has for example allowed for tissue-specific modeling of metabolic networks, as dependent e.g., on genomic, proteomic and metabolomics data (Chap. 14). Metabolic modeling is rapidly emerging as a powerful tool which can also help in the identification of targets for interventions as well as in the prediction of specific biomarkers (by predicting outgoing metabolic fluxes).

Not all metabolic functions can be conceptualized at the network level, however. For example, lipids are key building blocks of cellular membranes and lipoprotein particles. Changes of lipid levels in these structures lead to changes in their biophysical properties and thus also potentially affecting their function. While network-based modeling involves statistical inference as dependent on the network structure,

biophysical modeling requires *in silico* assembly of relevant molecular structures such as membranes by using, e.g., molecular dynamics simulations. As an example of such approach, recent study has shown that adipose tissue in obesity is characterized by enrichment of specific ether phospholipids containing arachidonic acid, despite the lower dietary intake of polyunsaturated fatty acids (Pietiläinen et al. 2011). Using a novel computational approach to simulate lipid plasma membranes based on lipidomics data, the study found that this lipid remodeling is part of an adaptive process, maintaining the normal membrane function but at the cost of higher vulnerability of adipose tissue to inflammation. Such an insight could not have been gained without considering the observed lipid changes in obesity at the level of their effect on cellular membrane properties. In general, modeling of lipid metabolism at biophysical and physiological levels is very challenging and an emerging area of systems biology. In this book, both topics are covered in Chap. 15 and 17, respectively.

## 2.3 Conclusions

In order to apply a systems approach to study specific disorders such as MetS, one needs three essential components: (a) a system, (b) experimental techniques, and (c) modeling techniques. These components are inter-connected by the so-called ‘systems biology cycle’ where measurements on a system are fed to a mathematical model, which is then further refined, leading to novel hypotheses and experiments etc. This book includes all three components, with the specific topics selected based on relevance to the study of MetS. Part II reviews ‘the system’ as relevant to MetS, which includes liver (Chap. 3), adipose tissue (Chap. 4), beta cell (Chap. 5), skeletal muscle (Chap. 6), central nervous system (Chap. 7), lipid metabolism (Chap. 8) and gut microbiota (Chap. 9). Selected emerging experimental techniques are introduced in Part III, including proteomics (Chap. 10), metabolomics (Chap. 11), fluxomics (Chap. 12) and *in vitro* colon model (Chap. 13). Part IV introduces specific modeling approaches which are particularly relevant to study MetS, including genome-scale metabolic modeling (Chap. 14), biophysical modeling of lipid membranes and lipoproteins (Chap. 15), methods of computational statistics (Chap. 16), and modeling of tissue cross-talk at the level of lipid metabolism (Chap. 17). Needless to say, the experimental and modeling techniques covered are not exclusive and some widely adopted approaches such as genomics are not explicitly included in this book. However, the methods covered in the book are particularly important if one is to adopt the physiological framework described in this chapter. How these techniques are connected into the ‘systems biology cycle’ ultimately depends on the questions asked and the specific system studied. Some practical examples will be provided in this book.

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