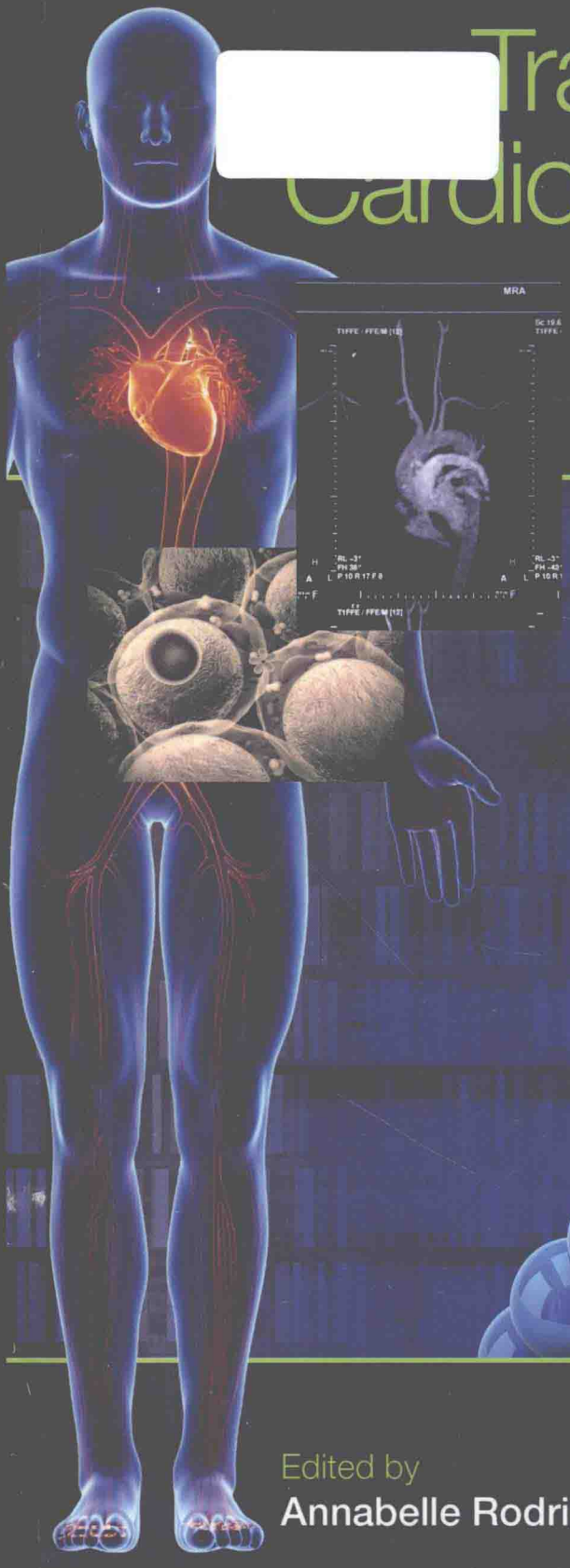
Translational Cardiometabolic Genomic Medicine



Edited by
Annabelle Rodriguez-Oquendo

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ANNABELLE RODRIGUEZ-OQUENDO

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1

Metabolomics and Cardiovascular Medicine

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1. INTRODUCTION

Cardiovascular disease is a complex, multifactorial disease that currently affects 1.5 billion people worldwide [1]. Many causative pathways through which risk factors act are still unclear. Metabolomics has recently emerged as a promising field that may help elucidate intricate details of the relationships between changes in human biology and complex cardiovascular disease phenotypes.

Metabolites are the end-products of metabolic processes occurring in cellular organelles. These are molecules smaller than 1 kDa ($1\ \text{Da} = 1.66 \times 10^{-27}$ kg). Historically, studies of metabolism have typically focused on a narrow range of metabolites or specific metabolic pathways. In contrast, metabolomics generally involves a more comprehensive assessment of many metabolites and pathways. The Metabolomics Society defines metabolomics as "comprehensive characterization of the small molecule metabolites in biological systems. It can provide an overview of the metabolic status and global biochemical events associated with a cellular or biological system" [2]. Similarly, Nicholson [3] defined metabolomics as a "quantitative measurement of the dynamic multi-parametric metabolic response of living systems to pathophysiologic stimuli or genetic modification..." [3]. The term "metabolome" was first coined by Oliver et al. [4] and Tweeddale et al. [5] in 1998. Fiehn et al. used the term "metabolomics" for the first time in 2001 [6]. Although the term was initially used in the literature pertaining to plants and agricultural research, with advancement in analytical tools and sample extraction methods, human and animal medical fields have also embraced these terms and approaches.

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A major advantage of studying the metabolome is that metabolites are generally considered to be molecular phenotypes much closer to clinical traits of interest—reflecting the integrated effects of both upstream molecular signals (e.g., genome, epigenome, transcriptome, and proteome) and environmental factors (e.g., diet, psychological stressors, microbiome, and environmental exposures—collectively referred to as the exposome). This concept was built on central dogma from the 1950s that there is a linear and unidirectional flow of information from genome to phenome. More recently, this concept has evolved into a complex network-based framework to account for multiple interconnected factors at all levels that determine a clinical phenotype. Nevertheless, the metabolome remains at the intersection of many factors that ultimately reflect or determine the health of an individual (Figure 1). Thus, it is essential to understand both the metabolome and its interactions with other -omics to apply metabolomics to practice.

The application of this concept in clinical and population research is still relatively new. However, already many important insights about the relationship between the metabolome and clinical cardiovascular disease have emerged, and several studies have identified key genome–metabolome associations that better characterize the molecular signals contributing to pathogenesis of atherosclerosis, hypertension, and other cardiovascular conditions. In this chapter, we provide an overview

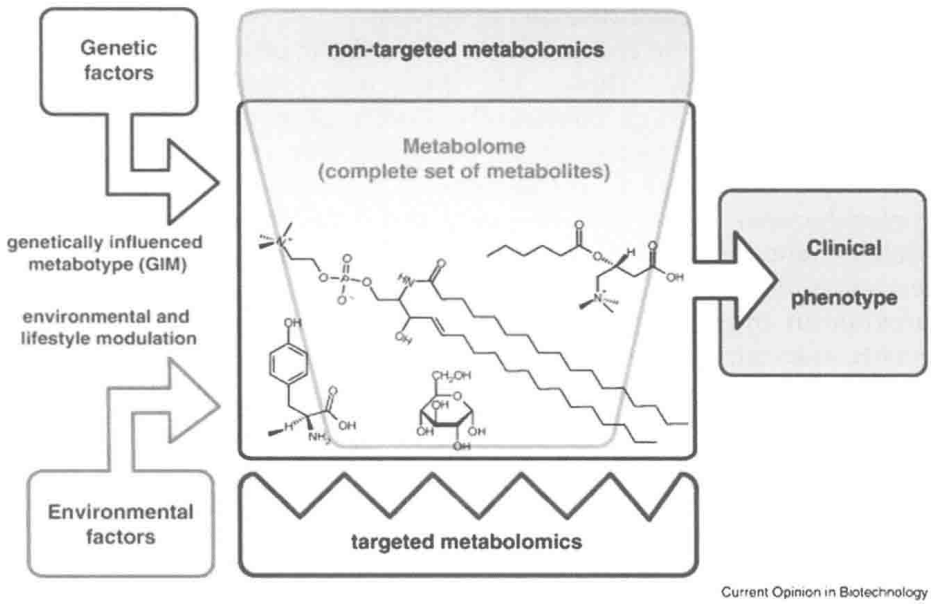

FIGURE 1 System biology network. *Adapted from Adamski et al. Curr Opin Biotechnol 2013; 24:39–47.*

of metabolomics trends and techniques, and review current understanding of the relationships among the metabolome, the genome, and the cardiovascular disease.

2. METABOLOMIC METHODS

A metabolomic study is composed of several discrete steps including bio-sampling, separation, metabolite detection, and data analysis (Figure 2). Each step is critically important to ensure valid and interpretable results.

2.1 Bio-specimen Selection and Handling

Particular attention should be given to the type of bio-sample and sampling techniques, as these determine the types of metabolites that need to be studied (Table 1). While collecting bio-samples, care must be taken to avoid degradation and contamination of collected sample. Some necessary considerations for sampling include timing (e.g., 24-h sampling versus collection after a 12- to14-h fasting period), sudden dietary changes (potentially interfere with the metabolome for over a week), bacterial or fungal contamination (especially for urine samples), medication intake (metabolites of medications may change the metabolome), diurnal variation in the hormones (anabolic and catabolic hormones vary during the day and may alter the metabolome), randomization, and transport and storage conditions of samples.

Serum is generally the preferred blood bio-specimen for metabolomic studies. This is because plasma retains fibrinogen and other coagulation cascade proteolytic enzymes that can continue to be active ex vivo and alter the metabolome or interfere with metabolite detection. Furthermore, ethylenediaminetetraacetic acid is typically used as the anticoagulant in plasma samples and can denature chromatograms and proteins in a way that may influence results. Serum has fewer potentially interfering coagulation cascade enzymes and proteins. However, even in serum there remain active enzymes that can continue to modify the metabolome ex vivo. To counteract these enzymatic processes, serum can be collected on ice. It is recommended to use samples stored at $-20\,^{\circ}C$ within 7 days and samples stored at $-80\,^{\circ}C$ within 1 month. However, in one report, changes in the metabolome were negligible after storage for 2.5 years [7]. In the case of repeated usage, fewer than three freeze–thaw cycles is advisable [7].

Until now, urine has been the most common sample for human metabolomics studies. It has many advantages, such as a noninvasive method of collection, lack of special preparation for collection, almost no

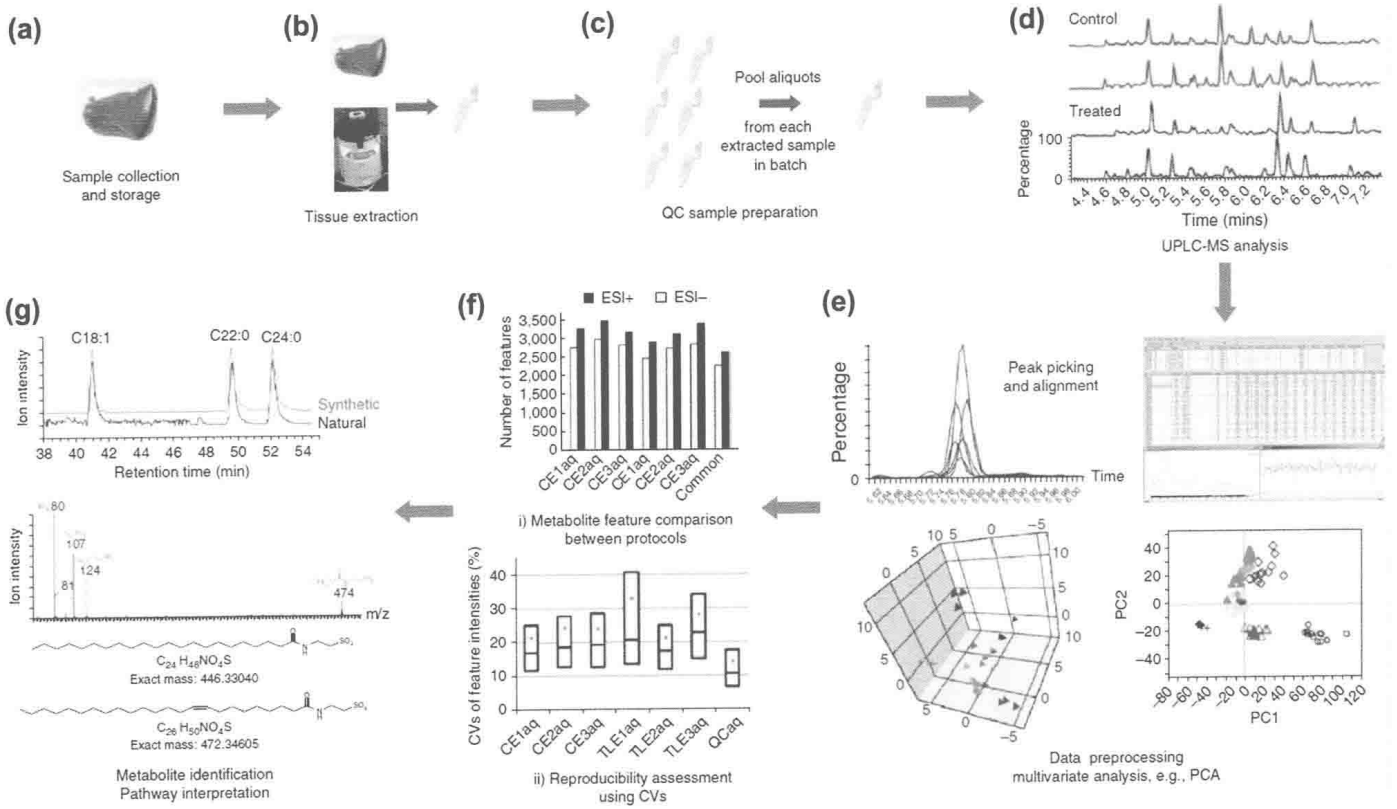

FIGURE 2 Schematic view of steps of a metabolomic study. *Adapted from Want et al. Nature Protoc 2013; 8:17–32.*