IJC Metabolic & Endocrine 9 (2015) 31–38

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Metabolomics, a promising approach to translational research in cardiology

Martino Deidda [a,*,1], Cristina Piras [b,1], Pier Paolo Bassareo [a], Christian Cadeddu Dessalvi [a], Giuseppe Mercuro [a]

[a] Dept. of Medical Sciences "M. Aresu", University of Cagliari, Asse didattico Medicina, SS Sestu KM 0,700, Monserrato, 09042 Cagliari, Sardinia, Italy
[b] Dept. of Biomedical Sciences, University of Cagliari, Cittadella Universitaria, SS Sestu KM 0,700, Monserrato, 09042 Cagliari, Sardinia, Italy

ARTICLE INFO

Article history:
Received 20 February 2015
Received in revised form 28 September 2015
Accepted 2 October 2015
Available online 5 October 2015

Keywords:
Metabolomics
Cardiology
Heart failure
Coronary artery disease
Hypertension
Diabetes
Obesity
Dislypidemia
Pediatric cardiology

ABSTRACT

The metabolome is the complete set of metabolites found in a biological cell, tissue, organ or organism, representing the end products of cellular processes. Metabolomics is the systematic study of small-molecule metabolite profiles produced by specific cellular processes. mRNA gene expression data and proteomic analyses do not show the complexity of physiopathological processes that occur in a cell, tissue or organism. Metabolic profiling, in contrast, represents a paradigm shift in medical research from approaches that focus on a limited number of enzymatic reactions or single pathways, with the goal of capturing the complexity of metabolic networks. In this article, we will provide a description of metabolomics in comparison with other, better known "omics" disciplines such as genomics and proteomics. In addition, we will review the current rationale for the implementation of metabolomics in cardiology, its basic methodology and the available data from human studies in this discipline. The topics covered will delineate the importance of being able to use the metabolomic information to understand the mechanisms of diseases from the perspective of systems biology, and as a non-invasive approach to the diagnosis, grading and treatment of cardiovascular diseases.
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1. Introduction

The "omics" sciences refer to a group of analytical methodologies that aim to achieve the collective characterization and quantification of pools of biological molecules, such as genes, transcripts, proteins and metabolites, which translate into the structure, function and dynamics of cells, tissues or organisms. Genomics can be described as a comprehensive analysis of DNA structure and function [1]. Understanding biological diversity at the whole genome level will provide insight into the origins of individual traits and disease susceptibility. Proteomics involves the systematic study of proteins to provide a comprehensive view of the structure, function and regulation of biological systems [2]. Genomics not only involves the study of single-nucleotide polymorphisms (SNP) and mutations in DNA, but it also includes, through the sub-discipline of transcriptomics, the complete analysis of gene expression in a cell. However, mRNA gene expression data and proteomics analyses do not show the complexity of the physiological and/or pathological processes that occur in a cell, tissue or organism. In contrast, the metabolomic approach represents a paradigm revolution in medical research, from a perspective that focuses on single pathways towards a holistic investigation that is able to capture the complexity of entire metabolic networks [3,4]. See Fig. 1

Metabolomics (or metabonomics) is the study of the metabolic profile of small molecules in a biological organism. The metabolome, in turn, is defined as the complete set of metabolites present in a cell, tissue, organ or organism [5] and represents all of the end products of cellular processes [3,4]. Metabolomics provides a functional view of an organism, as determined by the sum of its genes, RNA, proteins, and environmental factors including, for example, nutrition, medications and treatments. It reflects the true functional endpoints of biological events and is extensively used as a "functional-genomic" tool and in systems biology [3,4]. The philosophy underlying functional genomics is that a given "biologic" event should not be viewed as an isolated phenomenon but as a part of a complex network of changes, capable to interfere each other, within an organism; corollary of this affirmation is that in order to understand a biological event in all its complexity is necessary to measure as many entities as possible at any level of organization [3]. Specifically, metabolomics is the study of "… the complete set of metabolites/low-molecular-weight intermediates, which are context dependent, varying according to the physiology, developmental or pathological state of the cell, tissue, organ or organism…", while metabonomics has been defined as the "quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification", [6–8]. These two terms are

* Corresponding author at: Department of Medical Sciences "M. Aresu", University of Cagliari, Asse didattico Medicina, SS Sestu KM 0,700, Monserrato, 09042 Cagliari, Sardinia, Italy.
E-mail address: martino.deidda@tiscali.it (M. Deidda).
[1] Equally contributing authors.

http://dx.doi.org/10.1016/j.ijcme.2015.10.001
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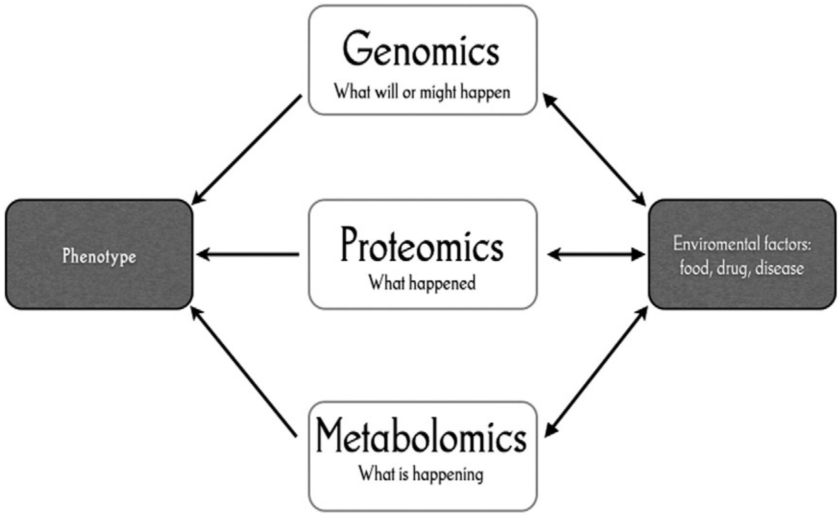

Fig. 1. From gene expression to phenotype. What "omics" tell us and how they interact.

currently used interchangeably and are becoming synonymous (See Fig. 2). In this paper, we prefer to use the term metabolomics to refer to either of the aforementioned meanings.

1.1. General aspects

As mentioned above, metabolomics is the measurement of multiple small-molecule metabolites in biological samples, including body fluids (urine, blood, cerebrospinal fluid, saliva, among others), tissues (heart, liver, kidney, brain, among others) and exhaled breath [9]. This technology is able to provide a comprehensive profile of the metabolic state of the whole organism, and it is linked to genetic settings and the influence of endogenous (i.e., hormones) and exogenous (i.e., food, drugs) substances or pathophysiological conditions. These stimuli induce a series of biochemical reactions that generate a wide and complex array of metabolites, many of which will be released in body fluids and tissues. Metabolomic analytical technologies can identify molecules with a relatively low molecular weight (<1000 Da), including amino and fatty acids, nucleic acids, carbohydrates, organic acids, vitamins, polyphenols, lipids, intermediates of many biochemical pathways, and inorganic and elemental species. The analysis of human biological samples provides characteristic numbers of metabolites, depending on the biofluid or tissue under examination and the analytical instrumentation used, and they can reach values in the thousands. The Human Metabolome Project [10], that has the aim to identify, quantify, catalog and record all metabolites potentially found in human specimens, have already

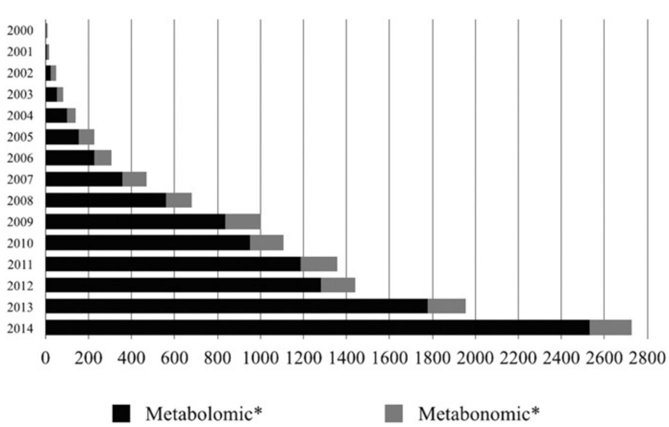

Fig. 2. The increasing number of publications covering the following search terms: Metabolomic* or Metabonomic*.

identified over 40,000 metabolites, stored in the Human Metabolome Database [11].

The metabolomic approach consists of two sequential steps:

- The sample is analyzed using an experimental technique that is suitable for providing a detailed molecular fingerprint, i.e., the full complement of low-molecular-weight metabolites; and 2) the data analysis is performed to identify and quantify the correlation between the identified species and the metabolic processes under investigation.

1.2. Experimental techniques

Among many different technological platforms, such as infrared and fluorescence spectroscopy and Coulombic arrays, nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) have been successfully used in the metabolomics field (Table 1), but the most commonly used are certainly the last two [3]. The NMR technique provides a detailed molecular picture of the biological sample. It simultaneously detects, in a non-targeted manner, signals from many different compounds, such as carbohydrates, amino acids, organic and fatty acids, amines, and lipids, without any initial sample pretreatment. In the NMR spectrum (See Fig. 3), each metabolite generates its own specific signals (often referred to as resonances). Each resonance displays a fine structure that can be directly related to the relative position of the different chemical groups in the chemical structure of the metabolite. The resonance intensity is proportional to the number of nuclei under observation generating that specific resonance, and to the molar concentration of the metabolite. Mass spectrometry, which is typically combined with a high-resolution separation technique like gas chromatography (GC) or liquid chromatography (LC), discriminates the molecules present in a biological sample according to their mass-to-charge ratio. Each of the peaks in the resulting chromatogram is associated with the characteristic mass spectrum of the metabolite (See Fig. 4), allowing their identification. NMR and MS have different advantages and limitations, and they are often regarded as complementary techniques. NMR provides a relatively fast but detailed analysis of the molecular composition of the sample with a (usually) rather simple preparation. The experiments are highly reproducible; the technique is non-destructive and represents a universal detector for all of the molecules containing NMR-active nuclei. However, NMR spectroscopy has some major drawbacks, mainly concerning the relatively low sensitivity when compared to other analytical techniques and the high management costs. On the other hand, MS techniques are highly specific and

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