Pharmacological Reports 66 (2014) 956–963

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Potential of metabolomics in preclinical and clinical drug development

Baldeep Kumar, Ajay Prakash, Rakesh Kumar Ruhela, Bikash Medhi *

Department of Pharmacology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

ARTICLE INFO

Article history:
Received 1 March 2014
Received in revised form 3 June 2014
Accepted 10 June 2014
Available online 24 June 2014

Keywords:
Drug
Metabolomics
Metabolism
Toxicology
Pharmacology

ABSTRACT

Metabolomics is an upcoming technology system which involves detailed experimental analysis of metabolic profiles. Due to its diverse applications in preclinical and clinical research, it became an useful tool for the drug discovery and drug development process. This review covers the brief outline about the instrumentation and interpretation of metabolic profiles. The applications of metabolomics have a considerable scope in the pharmaceutical industry, almost at each step from drug discovery to clinical development. These include finding drug target, potential safety and efficacy biomarkers and mechanisms of drug action, the validation of preclinical experimental models against human disease profiles, and the discovery of clinical safety and efficacy biomarkers. As we all know, nowadays the drug discovery and development process is a very expensive, and risky business. Failures at any stage of drug discovery and development process cost millions of dollars to the companies. Some of these failures or the associated risks could be prevented or minimized if there were better ways of drug screening, drug toxicity profiling and monitoring adverse drug reactions. Metabolomics potentially offers an effective route to address all the issues associated with the drug discovery and development.

Contents

Abbreviations: ADR, adverse drug reaction; ALS, amyotrophic lateral sclerosis; COMET, Consortium for Metabonomic Toxicology; FTIR, Fourier transform infrared; GC, gas chromatography; H-D, hydrogen-deuterium; HMDB, Human Metabolomic Database; HPLC, high pressure liquid chromatography; IEMs, inborn errors of metabolism; MS, mass spectrometry; NMR, nuclear magnetic resonance; PCA, principal component analysis; PD, Parkinson's disease; PLS-DA, partial least squares discriminant analysis; TMAO, trimethyl-amine N-oxide.

* Corresponding author.
E-mail address: drbikashus@yahoo.com (B. Medhi).

http://dx.doi.org/10.1016/j.pharep.2014.06.010
1734-1140/

Introduction

From the last 20 years, the drug discovery and development process has become more and more expensive as well as risky. The 'old' testing or screening methods often fail to identify many false molecules at the early stage of drug discovery. There is a need for the development of new methodologies which will help in better understanding of altered genetic expression and cellular changes as metabolic markers and link these to the altering pathophysiology [1–3]. Metabolite can be defined as a substance (<1500 Da) produced from the chemical changes of either food or medication by the body. Some examples of metabolites include peptides, oligonucleotides, sugars, nucleosides, organic acids, etc. Metabolome can be defined as the quantitative collection of all the low molecular weight molecules (metabolites) present in cells in a particular physiological state and thus reflecting the cell's status at that time. Metabolomics came into picture after the serial success of omics, i.e. genomics, transcriptomics and proteomics (Fig. 1). It is comparatively more precise and gives more informative data about the small metabolic molecules synthesized by the organism. Metabolomics approach was first originated at Imperial College London and has been used in disease diagnosis and toxicological studies [4]. Metabolomics helps in studying the treasury of endogenous small molecules present in organism. It is a complete analysis of the metabolome under a given set of conditions [5]. It is the only useful tool which tells us about the interactions between the genome, proteome and the external environment and provides the information about the sum total of all metabolic processes including anabolism and catabolism, and the related cellular processes such as absorption, distribution, and detoxification, signal transduction and regulation. It gives a direct picture of the cell's activity and its surrounding environment status in various conditions reflecting health, disease and the effects of drugs and the environment factors [5]. Metabolomics can be defined as the quantitative assessment of the metabolic responses of a biological system (cell, tissue, organ or biological fluids) at a particular time and to measure the changes in the metabolic response when exposed to any pathophysiological stimuli and/or genetic alterations. It is an emerging and rapidly evolving science and technology system of comprehensive experimental analysis of metabolic profiles for diverse applications in disease diagnosis, toxicology, disease progression and genetic modification of specific organisms, drug discovery and development and clinical practice [6–10]. Studying the effects (therapeutic or adverse effects) of drugs or disease progression on whole organisms by metabolomics relies on multiparametric quantification of metabolic alterations over time in response to a drug or stressor [2]. Currently, the medical researchers are focusing on studying the biochemical, cellular and molecular alterations in the body in response to any disease or environmental stimuli. This could be helpful in developing the customized approaches for diagnosis as well as treatment.

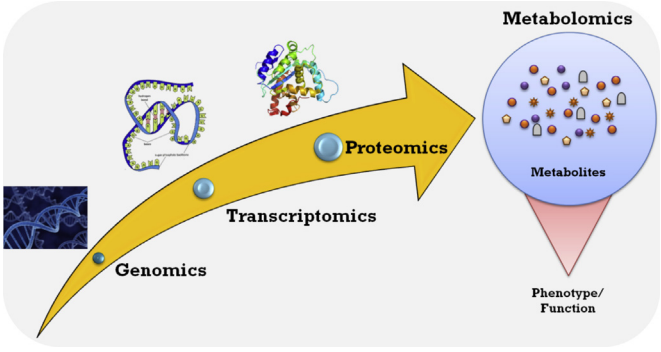

Fig. 1. Various 'Omics' and their interaction.

Metabolic profiling has offered a boost in the field of toxicology and drug development. It gives the more rapid and reproducible information about the drug metabolism and toxicity in preclinical and clinical development phases as compared to traditional methods.

If we look at the technologies used for studying the metabolome, various high throughput techniques/methods are being used for detection and quantification of the small molecule metabolites present in an organism. Its unique focus on small molecules and the physiological effects of drugs on these small molecules aligns the field of metabolomics towards the interests of many pharmaceutical researchers. Metabolomics requires the correlation of the chemical information with both biochemical and physiological consequences in order to achieve the specific objectives [11].

Over the last decade, the field of metabolomics has rapidly growing with potential applications such as pathophysiology, disease diagnosis, functional genomics, pharmacology, toxicology, foods and nutrition. Many studies have already reported the metabolic profiles of several diseases including type 2 diabetes, hypertension, pre-eclampsia, hepatic pathologies, prostate and colon cancer, Huntington's disease, motor neuron disease and depression [12].

Analytical technologies used for metabolomics studies

Metabolomic studies consists of two sequential phases: (1) an analytical technique that is designed to study the full profile of low molecular weight metabolites in a biological sample to generate an all-inclusive spectrum; (2) followed by data analysis and interpretation [13].

Metabolomics crucially depends on analytical technologies in order to identify, quantify and characterize the small molecules/metabolites in cell and organism. The principal techniques used for identification and characterization of metabolic profiling are nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectrometry (MS). Particularly, ^{1}H NMR spectroscopy is widely used technique for the identification and characterization of metabolites in biological fluids such as plasma and urine [2]. NMR is useful for detection of the molecules in low concentrations (lower limit of detection $\geq$1 μmol/L). It allows the identification of compounds through the comparative analysis of chemical shifts or J-coupling patterns. Unlike mass spectrometry, this technique (NMR) does not require prior separation or chemical derivatization of components, to analyze the complex mixtures [14]. Afterwards, mass spectrometry is a highly sensitive technique (lower limit of detection <1 pmol/L) used for the identification and quantification of small molecules on the basis of their molecular weight, fragmentation patterns and chromatographic retention times [15]. MS requires a prior separation of the metabolic components in case of complex mixtures using either gas chromatography (GC) or liquid chromatography (LC). Currently, different techniques (for separation and identification) are used in combination for better resolution, such as LC–MS and GC–MS. The combination of other instrumental techniques such as LC–MS-NMR has become widely useful for separation, dramatization and characterization of small molecules/metabolites. For the improvement of structural analysis and better interpretation of tandem mass spectroscopy (MS/MS) fragmentation data, Hydrogen-deuterium (H-D) exchange methods can be used in combination with MS [5,16].

Other techniques used for metabolomic analysis include Fourier transform infrared (FTIR) spectroscopy, Raman spectroscopy or electrochemical array detection [17]. Most of the detection