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Metabolomics and its Value in Today's Era

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Abstract

Metabolomics is the newly emerging field of 'omics' research.Its Comprehensive and simultaneous systematic determination of metabolite levels in the metabolome and their changes over time.This review outlines how metabolomics is emerging in today's life. It presents metabolomics methodology and focuses on the current and potential applications of metabolomics in different diseases with particular attention to its use as a biomarker in diagnosis, prognosis, and therapeutic evaluation. We think this review will appeal to both translational researchers and clinicians as it reviews up-to-date evidence on the utility of metabolomics, an often poorly understood topic. The report also highlights the use of metabolomics in maximizing and sustaining revenues post-marketing and in the development of clinical diagnostics.

Keywords: Metabolomics; Biomarker; Diagnostics; Therapeutic; System biology

Introduction

The 'omics' measurement platforms developed in the 1990s preceded the emergence of software platforms. The primary platforms in use are mass spectrometry and microarrays which associate tools to process data flows [1]. If we look at the bibliography, history started with database building and microarray processing; both terms 'systems biology' and 'platform' in bioinformatics occur with the emergence of large databases of high-throughput data and pathways availability [2]. The Metabolome represents the collection of all metabolites in a biological organism, which are the end products of its gene expression. Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind" - specifically, the study of their small-molecule metabolite profiles [3]. The word metabonomics is also used, particularly in the context of drug toxicity assessment. There is some disagreement over the exact differences between 'metabolomics' and 'metabonomics'; in general, the term 'metabolomics' is more commonly used. Metabolomics, or metabonomics as it is sometimes called, is a relatively new field of "omics" research concerned with the high-throughput identification and quantification of the small molecule metabolites in the Metabolome (i.e. the complete complement of all small molecule metabolites found in a specific cell, organ or organism). It is a close counterpart to the genome, the transcriptome and the proteome. Together these four "omes" constitute the building blocks of systems biology [4] (Figure 1).

Metabolomics for phenotyping and diagnostics in mammals and humans

Metabolic phenotypes are the products of interactions among a variety of factors like dietary, other lifestyle/environmental, gut microbial and genetic. Metabolomic profiling for identification of novel potential biomarkers in cardiovascular diseases. Metabolite concentrations represent sensitive markers of both genomic and phenotypic changes [5]. Previous studies of properties of metabolic works have mainly focused on the statistic properties of networks, including the small world, and power-law distribution of node degree, and building block of network motifs [6]. The gap of the post-genomic era is increasingly being filled by the metabolomics approach, comprising a technology for analyzing small molecule endogenous metabolites in complex biological samples. This new analytical science has progressed within the last years particularly with regard to improvements in mass spectrometry based detection, now allowing highly robust, reproducible, selective and sensitive qualitative or quantitative analysis of endogenous metabolites [7]. Microsatellites are the small DNA sequences with a tandem repetition of a particular motif of size 1-6. Microsatellites are found in all known genomes and play a significant role in many fields including DNA Fingerprinting, Population Studies, Forensics, Paternity Studies, Gene Regulation, Genetic Disorder Studies, and Evolution of Genomes. Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and affects 1 in 1,000 individuals. Using

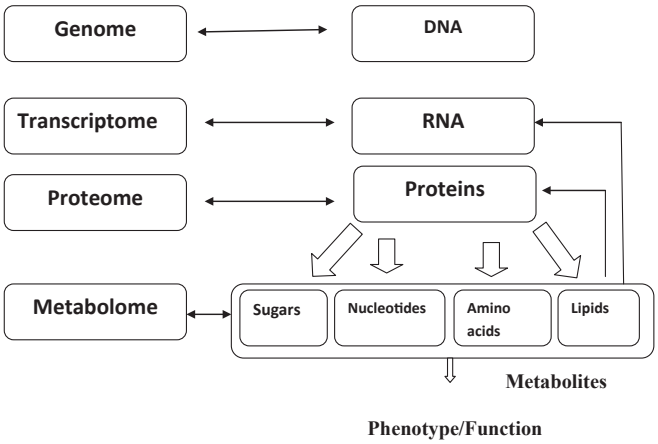

Figure 1: A Overal metabolomics structure with lipids as part of Metabolomics.

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functional score analysis and the KEGG pathway database, It has been identified several biologically relevant metabolic pathways which are altered very early in this disease, the most highly represented being the purine and galactose metabolism pathways. Several specific candidate biomarkers and pathway components, once extended to human disease, may prove useful for diagnosing cystic kidney diseases. Thus, urine metabolomics has great diagnostic potential for cystic renal disorders [8]. Phylogenetic analysis can be carried out based on either nucleic acid or protein sequences [9]. Metabolomics represents a paradigm shift in metabolic research, away from approaches that focus on a limited number of enzymatic reactions or single pathways, to approaches that attempt to capture the complexity of metabolic networks. Additionally, the high-throughput nature of metabolomics makes it ideal to perform biomarker screens for diseases or follow drug efficacy. one study has been revealed that the use of novel functional-genomic tools to study metabolism provides a unique insight into cardiac disease progression [10]. The metabolomes of medicinal plants are particularly a valuable natural resource for the evidence-based development of new phytotherapeutics and nutraceuticals. Comparative metabolomics platforms are evolving into novel technologies for monitoring disease development, drug metabolism, and chemical toxicology [11]. The ultimate goal of metabolomics is to achieve a comprehensive and quantitative analysis of all the metabolites in a biological system, and to achieve the closest possible approximation of its physiology. Metabolites in a sample possess very diverse biochemical properties, and are present at varying abundance levels [12]. In plant science, the present metabolomics technology cannot be considered a universal tool to perfectly elucidate perturbations imposed on sample plants although this is desired by plant physiologists [13]. In mammals, the potential of metabolomics is enormous, particularly with respect to studying the interface between our chemical universe and human biology. Humans are probably exposed to some 1–3 million discrete chemicals in our lifetimes, and most of these xenobiotic are metabolized in the body to render them less toxic. However, in a significant number of cases, the detoxication apparatus renders a xenobiotic more chemically reactive potentially more toxic, and, in some cases, carcinogenic. Understanding the role of human genetic differences in xenobiotic metabolism and its relationship to interindividual susceptibility to chemical toxicities and carcinogenesis is an area of intense interest [14]. Type 2 diabetes is caused by a complex set of interactions between genetic and environmental factors. Recent work has shown that human type 2 diabetes is a constellation of disorders associated with polymorphisms in a wide array of genes, with each individual gene accounting for <1% of disease risk. Metabolomics can provide certain advantages relative to other "omics" technologies (genomics, transcriptomics, proteomics) in diabetes research [15]. Development of the high throughput computational methods for the detection of SNPs (Single Nucleotide Polymorphism) and small indels (insertion / deletion) has gained wide applications in the field of the molecular markers [16]. Proteins directly interacting with each other tend to have similar functions and be involved in the same cellular processes. Mutations in genes that code for them often lead to the same family of disease phenotypes. Efforts have been made to prioritize positional candidate genes for complex diseases utilize the protein-protein interaction (PPI) information. But such an approach is often considered too general to be practically useful for specific diseases [17]. A kinetoplastid-specific KMP11 protein is well conserved among kinetoplastids and plays an analogous role in all the flagellates, irrespective of their pathogenicity in humans [18]. The genome sequence information is essential to understand the function of extensive arrangements of genes. It is significant to combine all sequence information in a precise database to provide an efficient manner of sequence similarity search [19]. The performance of most methods for cancer diagnosis using gene expression data greatly depends on careful model selection [20]. Cancer susceptibility may be controlled not only by host genes and mutated genes in cancer cells, but also by the epistatic interactions between genes from the host and cancer genomes [21]. Damage analysis in metabolic pathways is one of the most highlighted fields in systems biology area. Metabolic errors are studied with respect to inherited enzyme deficiencies. The damages usually occur due to changes in a particular enzymatic reaction or deletion of a step. Some enzyme disorders can also cause the particular reaction not to occur causing accumulation or reduced presence of a metabolite [22]. Several Omics methods have been applied to identify virulence genes, i.e., DNA microarrays, In Vivo Expression Technology (IVET), Signature-Tagged Mutagenesis (STM), Differential Fluorescence Induction (DFI), etc [23,67,68] (Figure 2).

Application to bioscience

The application of metabolomics is growing rapidly but many challenges must first be addressed before it can reach its true potential. Metabolomics organizations are currently working towards guidelines for commonality in metabolomics experiments as development of optimal methodologies and study designs are needed. Mass spectrometry (MS) in combination with liquid chromatography (LC), *i.e.* LC-MS, is the key analytical technique on which the emerging "omics" technologies of proteomics, metabolomics and lipidomics are based. There is rising death of humans worldwide by reason of tuberculosis. The current sequencing of the Mycobacterium tuberculosis genome holds assure for the development of new vaccines and the design of new drugs. In this view, the functions prediction of genomic sequences for hypothetical proteins will invigorate our knowledge with reference to the identification of new drugs for tuberculosis [24]. Mass spectrometry (MS) MS based metabolomics is increasingly used to characterize the complex metabolic effects of nutrients or foods. Metabolomics, the global profiling of metabolites in different living systems, has experienced a rekindling of interest partially due to the improved detection capabilities of the instrumental techniques currently being used in this area of biomedical research. Metabolomics have been used in toxicology, plant physiology, and biomedical research. quality-weighted statistics leads to more accurate gene expression measurements and more sensitive detection of their changes with significantly lower type II error rates [25,70]. The

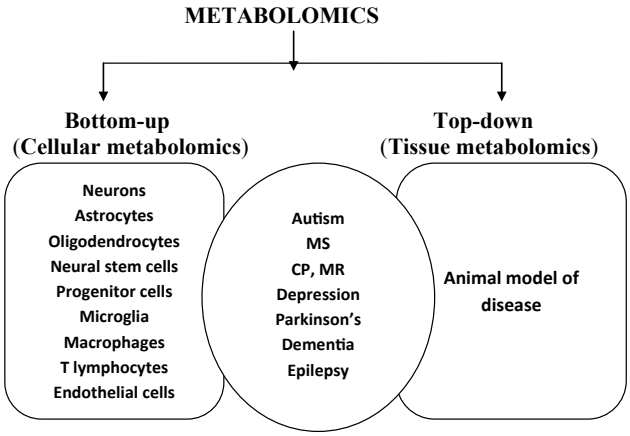

Figure 2: Metabolomics particularly useful for disorders.

analytical methods of choice for the analysis of metabolites in search of disease biomarkers in biological specimens. Global metabolite analysis and profiling of two different sets of data results in a plethora of data that is difficult to manage or interpret manually because of their subtle differences [26,64]. The booming bioinformatics studies, especially the microRNA (miRNA) microarray analysis, have significantly accelerated the uncovering of underlying mechanisms of human diseases [27,71]. Phenotypic expression of renal diseases encompasses a complex interaction between genetic, environmental, and local tissue factors. The level of complexity requires integrated understanding of perturbations in the network of genes, proteins, and metabolites. Metabolomics attempts to systematically identify and quantitate metabolites from biological samples. The small molecules represent the end result of complexity of biological processes in a given cell, tissue, or organ, and thus form attractive candidates to understand disease phenotypes [28]. During the previous decade, a new array of analytical methodologies and technologies were introduced related to the analysis of microbial, plant and animal metabolomes [29,65]. Plant metabolites are characterized by an enormous chemical diversity, every plant having its own complex set of metabolites. This variety poses analytical challenges, both for profiling multiple metabolites in parallel and for the quantitative analysis of selected metabolites [30]. Selective amplification of nucleic acid molecules, that are initially present in minute quantities, provides a powerful tool for analyzing nucleic acids [31,66]. Current technology allows for comprehensive and rapid mRNA expression profiling and mass spectrophotometric measurement of low molecular weight intermediates and metabolic products. In prokaryotic organisms, this combination provides a potentially powerful tool for identifying gene function and regulatory networks even in the absence of a combined proteomic approach [32,62,63]. One of the researches has been focused on metabolites that these are essential for the growth and survival of the relevant bacteria. To identify potential drug targets, they have to be further screened these metabolites to eliminate any found in the human host [33]. Domains of modern computational science are converging on complex problems in the general field of systems biology. There is now a credible possibility of modeling drug delivery vesicles (liposomes) and their properties with qualitative and quantitative insight coming from atomistic calculations [34]. Delta Hepatitis currently infects about twenty million people worldwide which is most common among populations using injectable drugs particularly in countries bordering the Mediterranean Sea while least common in Eastern Asia. The disease is caused by HDV.HDV is a subviral satellite of hepatitis B virus, on which it is dependent for its envelope proteins [35,67]. The study was undertaken to model and validate the small delta antigen protein of HDV the predicted model is useful to develop new inhibitor against HDV [34,35]. Whole genome sequences of the four strains of *Streptococcus pneumoniae*, encapsulated TIGR4, D39, G54 and non encapsulated R6 are considered for the comparative study on genome features, whole genome pairwise alignment, gene role category, and virulence factors using relevant comparative genomics tools [36,61]. DNA vaccines have been used with great success in experimental and some clinical therapy. However, the mechanisms of activation of the immune system by these vaccines are not utterly understood yet [37]. *Alpheus* is an analysis pipeline, database and visualization software able to detect several types of variants, including non-synonymous and synonymous single nucleotide polymorphisms (SNPs), insertions/deletions (indels), premature stop codons, and splice isoforms [38,62]. Viral Microsatellite Database (VMD) currently hosts microsatellites of around 3500 viral genomes along with their alignments, locus information, imperfection info, protein info etc [39]. The availability of the complete sequence information of *Neisseria meningitides* serogroup B proteome has made it possible to carry out the *in silico* analysis of its genome for identification of potential vaccine and drug targets [47]. Hypoxanthin-guanine phosphoribosyl transferase (HPRT) is responsible for catalyzing a reaction which breaks down uric acid in the body. The lack of this enzyme creates a build-up of uric-acid, leading to a neurological problem, joint pain and kidney problem [40]. The amount of glycomics data being generated is rapidly increasing as a result of improvements in analytical and computational methods [41,63]. Service-Oriented Architecture (SOA) is being one of the widely accepted methodologies in software market for building and integrating different kinds of software systems [42]. Short interfering RNAs (siRNAs) can be used to suppress gene expression and have a lot of potential applications in therapy, yet how to design an effective siRNA is still under consideration [43]. Virtual screening by molecular docking has become a largely used approach to lead discovery in the pharmaceutical industry when a high-resolution structure of the biological target of interest is available [44,58]. Quantification of the metabolic network of an organism offers insights into possible ways of developing mutant strain for better productivity of an extra-cellular metabolite. Computational systems biotechnology was therefore, made a platform to experimental techniques for producing commodities with a low cost, good quality and quantity, and fastens the fermentation processes in industry [45]. The relative rates of development of the high throughput computational methods for the detection of SNPs (Single Nucleotide Polymorphism) and small indels (insertion / deletion) has gained wide applications in the field of the molecular markers [36]. Completed genome sequences are rapidly increasing for Rickettsia but most the genes in them does not have an assigned function. One study has revealed by on identifying the function of hypothetical proteins of *Rickettsia massiliae* MTU5 that were conserved in Rickettsia species [46]. The genomic projects have provided a far wide amount of information that still requires be analyzing and interpreting [47]. From a medical perspective, the characterization of the microbial composition of the skin surface, oral cavity, and gut in both healthy and diseased people enables a comparison of microbial community profiles and also contributes to the understanding of the potential impact of a particular microbial community. Hepatitis B virus is a human infectious disease universally caused by the hepatitis B virus. Immunoinformatics tools have been used to predict the epitopes from seven putative protein viz. polymerase, large-S- and middle –S- Protein, S and X- protein, Precore/Core Protein, Core and E- antigen. These epitopes showed highest binding score at optimum threshold. Epitopes may use as an antigen for diagnosis and also might be helpful for designing peptide based subunit vaccine against Hepatitis B virus [48,59]. The cation-π interaction is an important, general force for molecular recognition in biological receptors. In a study, It has analyzed the energy contribution resulting from cation-p interactions in the set of therapeutic proteins [49]. Biological Engineering involves global DNA sampling and modular design from genetic parts. A new approach reflected by natural history is based on the recognition of interchangeable DNA fragments that move around the world due to horizontal gene transfer. According to the large scale, metagenomics provide opportunities to sequence whole genomes within environmental populations. Annotated gene sequences, protein structures, and metabolic data can be used to design small biosystems from interchangeable genetic parts, the same as from functional modules [50]. By combining metabolomics technology and genome data analysis, it is possible to replace empirical target-selection strategies with a more scientific approach. All steps of

biotechnological development, from up-stream and mid-stream to down-stream processes will benefit significantly by taking systems biotechnological approaches. A notable success has been made on designing optimized production systems that maximize productivity and minimize raw materials costs for valuable metabolites. A remarkable advantage of this approach up-to-data and its relevant web resources is critically reviewed in this article. Indeed, this alternative approach will not only hopefully be useful for improving the productivity of many meaningful metabolites including antibiotics, enzymes, organic acids, etc. from industrially significant microorganisms but also will ensure correlation of many experimental reliabilities [51,57]. Antibiotic discovery aimed at conventional targets such as proteins and nucleic acids faces challenges from mutations and antibiotic resistance. Small molecule metabolites, however, can be considered resistant to change, as they do not undergo rapid mutations. Developing analogs or scavengers of essential microbial metabolites as antibiotics is a promising strategy that can delay drug resistance. One study has revealed previously unexplored targets along with metabolites that are well established in antibiotic discovery. Identification of established metabolites strengthen our analyses while the newly discovered metabolites could lead to novel antimicrobials [52,60].

Future Direction in Metabolomics

- The Future of Metabolomics provides detailed insight into the effective use of metabolomics throughout drug discovery, preclinical development and clinical trials.
- Metabolomics can be applied in lifecycle management by identifying new indications for a marketed product, or by developing a test that will optimize dosing and help patients to receive a dose that is both efficacious and safe.
- Metabolomics can be used to uncover new drug targets, prioritize lead compounds, and assess toxicity non-invasively, enabling the development of novel, smarter and safer drugs.
- Within the next 10 years it is anticipated that metabolomics will become a standard tool in the pharma industry as validated metabolomic-based biomarkers begin to emerge and cost-effective screens are established.
- Metabolomics is the best technology for the analysis of large mutant or transgenic libraries of model experimental plants, such as Arabidopsis, rice, etc.

Conclusion

Metabolomics has its roots in early metabolite profiling studies but is now a rapidly expanding area of scientific research in its own right. Metabolomics (or metabonomics) has been labeled one of the new"omics", joining genomics, transcriptomics, and proteomics as a science employed toward the understanding of global systems biology. In the postgenomic era, metabolomics is expected to be the newest useful omics science for functional genomics. We believe this to be an important and interesting topic that bridges preclinical and clinical oncology. Here, It is reviewed the current and potential applications of metabolomics, focusing on its use as a biomarker. Use up-to-date case studies to understand current and future directions in the application of metabolomics. Metabolomics has the potential to influence different disorder affecting patient care with benefits already being seen with the use of metabolite imaging in breast and prostate cancer diagnosis and probable future uses as a biomarker for early cancer diagnosis, determination of treatment efficacy, and in developing novel therapeutic to drug discovery and development, explore potential cost savings, and recognize lucrative partnering opportunities in this fast moving field.The rapid progress of biotechnology and biological data analysis methods has led to the emergence and fast growth of a promising field, namely, systems biology [53,54]. Being a relatively new addition to the 'omics' field, metabolomics is still evolving its own computational infrastructure and assessing its own computational needs [55,56].

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