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"Omics" in pharmaceutical research: overview, applications, challenges, and future perspectives

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[ABSTRACT] In the post-genomic era, biological studies are characterized by the rapid development and wide application of a series of "omics" technologies, including genomics, proteomics, metabolomics, transcriptomics, lipidomics, cytomics, metallomics, ionomics, interactomics, and phenomics. These "omics" are often based on global analyses of biological samples using high through-put analytical approaches and bioinformatics and may provide new insights into biological phenomena. In this paper, the development and advances in these omics made in the past decades are reviewed, especially genomics, transcriptomics, proteomics and metabolomics; the applications of omics technologies in pharmaceutical research are then summarized in the fields of drug target discovery, toxicity evaluation, personalized medicine, and traditional Chinese medicine; and finally, the limitations of omics are discussed, along with the future challenges associated with the multi-omics data processing, dynamics omics analysis, and analytical approaches, as well as amenable solutions and future prospects.

[KEY WORDS] Omics; Genomics; Transcriptomics; Proteomics; Metabolomics; Target Discovery; Toxicity Assessment; Personalized Medicine; Traditional Chinese Medicine

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Introduction

During the late 20th century and early 21st century, the biological research has experienced many innovations from micro-level to macro-level, and finally a comprehensive description of life phenomena on various functional molecules has become a reality. The publication of the full human genome sequence in 2003 by the International Human Genome Sequencing Consortium is a crucial milestone in the history of genetic research, which has paved the way for "genome" and "genomics" research and initiated the so-called post- genomic era in biomedical research [1]. In post-genomic era, determining the primary sequences of informational macromolecules is no longer a limiting factor in deriving an ability to understand the biological functions of cells and organisms [2]. Consequently, the research focus has moved beyond the genome to the role of genes, which is a much more challenging task, including the understanding of gene transcriptional regulation, the biochemical functions of all the gene products and their interactions, and learning how they influence the chemicals that control cellular biochemistry and metabolism. Inspired by the terms "genomics", a number of words coined with the suffix "-ome" and "-omics" have appeared in the last two decades, such as transcriptomics, proteomics, metabolomics, glycomics, and lipidomics. Traditional biochemical methods are time-consuming and low-efficient, while omics technologies are based on global and high-throughput analytical methods, such as microarray, 2D-gel, and 2DLC/MS, producing large-scale data. By means of bioinformatics and computer modeling, omics is expected to provide many more additional insights and clues to the mechanisms of biological processes and functions, and thus may build up a theoretical framework of modern

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life science.

The post-genomic era signifies both the development of these omics technologies and their application to biomedical and pharmaceutical researches. Compared with the traditional research methods, omics allows for exploration of the genome, transcriptome, and proteome more broadly with greater sensitivity and resolution, and provides solutions for target discovery and validation, drug toxicity and safety assessment, pharmacology, molecular diagnosis and prognosis, and personalized healthcare, among other implications. Meanwhile, these omics technologies produce a vast amount of data, posing the challenge: how to deal with such complicated data? As an indispensable tool for omics, bioinformatics derives knowledge from the computer analysis of omics data, by retrieval and analysis of genetic code information, experimental results from various sources, patient statistics, and the scientific literature. Bioinformatics has developed a number of novel methodologies for processing, analyzing, and efficiently interpreting the omics data in the past 20 years, and the combination of omics and bioinformatics enables integral analysis on multiple omics data. It is generally accepted now that an efficient investigation on a biological process should be conducted with multiple viewpoints, for example, the view of cell-chromosome-DNA- RNA-protein- metabolite, which is just a strategy of systems biology.

So, is "omics" what used to be called biochemistry? Instead of analyzing individual components or aspects of the organism through routine biochemical methods, such as individual functional gene, protein or biochemical reaction, omics focuses on all the components and their interactions within a global site. Omics reflects the evolution of collective thoughts and data, and is often considered as the most essential part of systems biology. Nowadays, quite a number of high-throughput approaches have become routine for accumulating a wealth of omics-scale data, affording to different view of the cell-chromosome-DNA-RNA-protein- metabolite continuum (Fig. 1).

Omics data generally describe the 'wholeness' of biological systems and may provide no useful information directly or in detail. However, through bioinformatics analyses, some further useful information may be discovered, such as diagnostic biomarker(s), potential target(s), and key pathway(s), just name a few. Network biology is another important tool for omics data processing, especially for multi-omics data. Molecular network can visualize multi-omics data and reveal the relationships between various functional molecules, which is essential for a comprehensive understanding of a biological process from multiple perspectives. Public databases on the internet now play an increasingly important role in biological research, and bioinformatics bridges them to experimental omics data. Therefore, based on omics data, public databases, and molecular network, it is possible to view biological processes on pathway maps, protein interactions, functional ontologies, gene-disease associations, mechanisms of drug action, personalized medicine, and so on, which is also an aim of systems biology. Various omics, bioinformatics, systems biology, and other research methodologies are closely associated with each other, as shown in Fig. 1.

In the last two decades, omics has become an efficient tool for the global study of interactions between drugs and biologically functional molecules. Results on single drug-gene or drug-protein interactions are not sufficient to explain complex phenotypes, and it is necessary to understand drug responses at the level of entire system. Omics often denotes the study of an entire set of entities in a class, which may be known as "pharmacogenomics" [3], "pharmacotranscriptomics", "pharmacometabolomics", and "pharmacoproteomics" [4]. Herein the advances of omics technologies are reviewed, alongside with a brief historical and futuristic perspective of omics applications in pharmaceutical research, especially in the fields of drug target discovery, toxicity evaluation, personalized medicine, and traditional Chinese medicine.

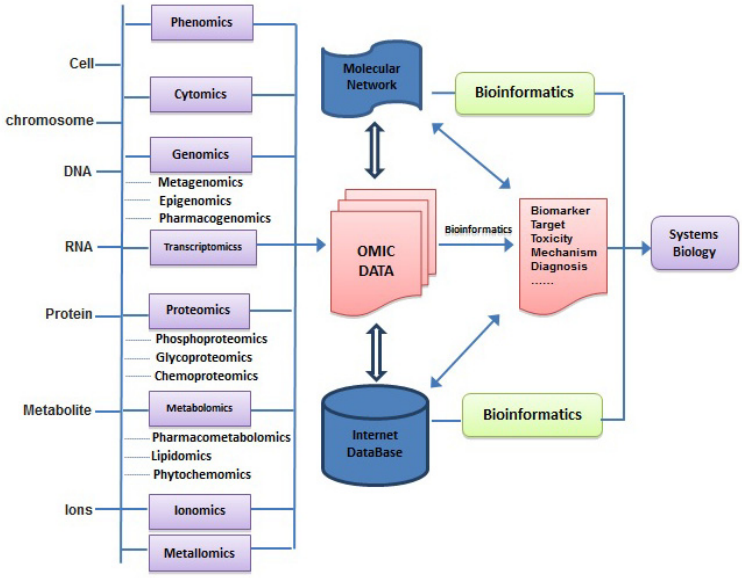

Fig. 1 Various omics techniques and their roles in systems biology

Overview of Omics Technologies

Genomics

Genomics is a genome-scale technology and can be applied in all areas of biological investigation. In general, research of genomics includes structural genomics and functional genomics. Structural genomics seeks to describe the three-dimensional structures of proteins encoded by a given genome, and allows for a high-throughput method of structure determination through a combination of experimental and modeling approaches. Even today, its major branch is still concerned with sequencing the genomes of various organisms, especially with patterns of gene expression under various conditions. Functional genomics attempts to describe gene and protein functions and their interactions. Microarrays and bioinformatics are the most important tools for genomics, such as the serial analysis of gene expression (SAGE), cDNA microarrays, DNA chip, and sequence tagged fragments display. Genomics is a broad concept that can be used in different research subjects, mainly including pharmacogenomics, metagenomics, and epigenomics.

Pharmacogenomics

Every person has a unique variation of the human genome, which leads to individual's different responses to drugs. Pharmacogenomics is the study on how genes affect a person's response to drugs, so as to develop effective and safe medications and determine doses to be used. It embraces the discovery of new disease-related genes and also the investigation on the effects of genetic factors on medication with the aim to predict the individual's clinical response. Adverse drug reactions are reported as a significant cause for hospitalizations and deaths in many countries [5]. Pharmacogenomics enables researchers to understand how inherited differences in genes affect the body's response to medications, which can be applied to predict whether the drug is effective orineffective and/or cause side effects for a particular patient. For instance,

McDermott and Benes [6] have applied pharmacogenomics to the discovery of new biomarkers of sensitivity and resistance to cancer therapeutics and proved the marked sensitivity of Ewing's sarcoma cells harboring the EWS-FLI1 gene translocation to poly (ADP-ribose) polymerase (PARP) inhibitors. Visscher *et al* [7] have reported the pharmacogenomic prediction of anthracycline- induced cardiotoxicity (ACT) in children, with multiple genetic variants in SLC28A3 and other genes (ABCB1, ABCB4, and ABCC1) being identified associated with ACT, which might be used to identify high-risk patients.

Metagenomics

The term "metagenomics" was first used by Handelsman and colleagues in 1998 [8]. It studies the collection of gene sequences from the environment in a way analogous to the study of a single genome. A large number of microorganisms exist in the gastrointestinal tract of humans and animals. It is reported that the gut bacterial population in humans is about 3 million genes, almost 150 times of the number of human genes [8], and that they are closely related to the physiological functions of the host. The first metagenomics study was conducted on a woolly mammoth (*Mammuthus primigenius*) sample using emulsion polymerase chain reaction and the pyrosequencing technique [9].

Microbial communities play a key role in preserving human health. Metagenomics has been widely applied in the research of obesity, providing evidence for the important role of intestinal microbiota for obesity. Ley *et al* have proven that, in obese rats, the proportion of Acteroidetes and Firmicutes in the cecum changes significantly [10]. Turnbaugh *et al* have observed analogous differences in the distal gut microbiota of obese versus lean individuals, and the relative abundance of Bacteroidetes increases as obese individuals lose weight [11]. A recent study of the gut microbiota of 123 non-obese and 169 obese patients has suggested that a high bacterial richness, particularly in eight species, protects against obesity [12]. Metagenomics studies have also demonstrated an imbalanced microbiota composition in various diseases, such as Crohn's disease [13], necrotizing enterocolitis [14], polyposis or colorectal cancer [15], and type 2 diabetes [16].

Epigenomics

Epigenetics refers to the heritable changes in gene expression without any alteration in DNA sequence. Epigenomics deals with the global analysis of epigenetic changes across the entire genome, in order to reveal the genetic information in addition to the DNA sequence which may affect gene function. Epigenetic regulation can be complemented by five different mechanisms: DNA methylation [17], histone post-translational modification [18], histone variants [19], RNA interference [20], and nuclear organization [21]. Methylation is the most common flexible genomic parameter that can change genome function under exogenous influence and usually occurs in CpG islands, a CG rich region, in the DNA (e.g., promoter regions, regulatory domains, and also in intergenic regions) [22]. The Human Epigenome Project (HEP) was started in October 2003 by the Human Epigenome Consortium, with the aim to identify, catalogue, and interpret genome-wide DNA methylation patterns of all human genes in all major tissues [23]. HEP is widely supported by cancer research scientists from all over the world. A number of studies have described DNA hypomethylation in several tumor types, such as colorectal and gastric cancers and melanomas [24]. Another important epigenetic alteration is histone modification in cancer cells, and it may affect the gene transcription through local relaxation of nucleosomal structure and through recruitment of non-histone proteins [25], which can be chemically modified by different enzymes at their external N- and C-terminal tails as well as at internal histone-fold domains.

Transcriptomics

The transcriptome is the set of all RNA molecules, including mRNA, rRNA, tRNA, and other non-coding RNAs produced in the cell, which is, unlike the genome, able to vary

under the influence of external environmental conditions. Transcriptomics investigates the way the whole transcriptome changes under a variety of biological conditions. The sequence of an RNA mirrors the sequence of the DNA from which it was transcribed, and the transcription process of RNA synthesis is the first step of gene expression; however, although the same genome exists in almost every cell in humans or other organisms, different cell types express different sets of genes. Retrieval of a transcriptome database can help researchers determine for each gene when and where it is turned on or off, providing clues to its possible function. Through the collection and comparison of different types of transcriptome from cells of healthy or diseased organisms, researchers may interpret the functional elements of the genome and gain a better understanding of the biological functions of cell types and their potential pathogenesis of diseases. Currently, approaches for transcriptome data acquisition and analysis are mainly based on chip technology, including cDNA microarray and oligonucleotide chips [26], serial analysis of gene expression (SAGE) [27], and massively parallel signature sequencing (MPSS) [28]. RNA-Seq is a recently developed approach to transcriptome profiling that uses deep-sequencing technology to reveal a snapshot of the presence and quantity of RNA from a genome at a given moment in time [29-31].

Transcriptomics allows for the discovery of some disease-related gene expression and thus is expected to be applied for clinical diagnosis. For example, Alzheimer's disease (AD) is observed with different normal neurons in the brain cell gene expression profiles on neurofibrillary tangles, and its transcriptome has emerged as a potential resource for the discovery of biomarkers for AD [32-33]. Transcriptomics is also meaningful for the diagnosis of diseases lacking a gold standard, such as autism [34]. Currently the diagnosis of autism relies on more than ten hours of clinical assessment in order to make a judgment, while by comparing the transcriptome differences between the normal population and patients, the disease-related specific expression can be discovered for the diagnosis of autism. Transcriptomics is also reported for personalized medicine [35] and in research on drug-induced toxicity [36], carcinogenesis [37-38], and stem cells [39].

Proteomics

The proteome is the entire set of proteins [40] produced or modified by an organism or system, which varies with genetic and environmental factors. Proteomics is the study of the proteome of a certain type of cell, tissue, or body fluid, particularly their structures and functions, at a large-scale, high-throughput, and systematic level [41-42]. Proteomics is a complement to the research of genome translation and modification and an efficient tool for the comprehensive understanding of genome expression.

With the development of related high-throughput analytical technologies and mass spectrometry, proteomics has been rapidly developed in various research fields. Two-dimensional gel electrophoresis (2DE) is a traditional approach in proteomics study and now still widely used. How to improve the capacity, sensitivity, resolution, and detection accuracy is the key issue of 2DE. 2D Fluorescence Difference Gel Electrophoresis (2-D DIGE) is a more efficient proteomics method, using narrow pH gradient gel separation combined with high sensitivity protein staining techniques [43-44]. Currently, two-dimensional chromatography with mass spectrometric detection (2DLC-MS) [45], two-dimensional gel electrophoresis-liquid chromatography with mass spectrometric detection (2DE-LC-MS) [46], capillary electrophoresis with mass spectrometric detection (CE-MS) [47], and other chromatographic techniques are increasingly being applied in proteomics. 2D LC-MS, for example, with the first dimensional separation according to the molecular size of the proteins and the second dimensional separation by reversed phase chromatography or strong cation exchange chromatography, is superior to 2D-gels due to its large separation capacity, high resolution, and fast speed. In recent years, 2D-LC and related technologies have been developed rapidly, and may become the major research method for proteomics in the future.

Mass spectrometry (MS) is another essential tool in proteome analysis. Traditionally, proteins are identified by sequence analysis. Due to the rapid development of MS techniques, target protein identification can now be quickly and efficiently realized with a small amount of sample (typically a few micrograms is sufficient). In addition, MS can also analyze proteins with post-translational modifications. According to the different ion sources, MS mainly includes matrix-assisted laser desorption time-of-flight mass (MALDI-TOF-MS), and electrospray ionization time-of-flight mass (ESI-TOF-MS), and besides TOF, the mass spectrometer also includes a quadrupole and ion trap mass spectrometer. Traditional 2DE-based analysis is inherently limited by low resolution, poor reproducibility, and serious bias factors. To overcome these restrictions on progress, quantitative proteomics was gradually developed. There are two strategies for proteome quantification: label-free methods [48] and stable isotope labeling methods, including ICAT [49], iTRAQ [50], and SILAC [51], which presently have become the most important techniques for quantitative proteomics.

Proteomics provides new ideas for research in the medical and life sciences and has produced remarkable achievements in the past two decades. In the field of cancer research,especiallyearly clinical diagnosis, a series of cancer-related proteins are discovered, such as cathepsin B [52], heat shock protein 27 [53], mRNA junction protein P62 [54], oral squamous cell carcinoma related protein of HPA/sAa/K-10/GA-HAS [55], and pfetin [56]. Drug development is the most promising field for the applications of proteomics. It can be used in the discovery and validation of drug targets, elucidation of mechanism of drug action, toxicology testing, and drug metabolic researches.

Phosphoproteomics

Phosphorylation is one of the most important post- translational modifications of proteins in the cell. Phosphoproteomics is a branch of proteomics to study those proteins containing phosphate groups as a post-translational modification. The phosphorylation of proteins regulates nearly every aspect of cell life from gene expression, signaling, and metabolism, to cell growth, division, differentiation, and development. Moreover, the dysregulation of protein phosphorylation may result in many human diseases, most notably cancer, diabetes, heart disease, and Alzheimer's disease.

In recent years, the development and application of proteomics provides technological support for the qualitative, quantitative, and functional studies on phosphorylated protein, and make it possible to systematically study protein phosphorylation on a large scale. The identification and detection of phosphorylated proteins are the key technologies in phosphoproteomics research. Technologies applied in phosphoproteomics include diphase phosphate polypeptide spectra (2D-PP), two-dimensional gel electrophoresis (2DE), two-dimensional high-performance liquid chromatography (2D-HPLC), and immobilized metal affinity chromatography (IMAC). Phosphorylated proteins are isolated and enriched and then structurally identified or directly analyzed by LC/MS.

Phosphoproteomics plays an important role in the study of disease pathogenesis and pharmaceutical research, in which it can be applied to the discovery of targets, especially phosphorylated targets [57-58]. In addition, phosphoproteomics can be used for the screening of potential diagnostic or prognostic markers by comparing the abundance of protein phosphorylation between patients and healthy subjects. Meanwhile, protein phosphorylation is a highly dynamic process and is very sensitive to the use of drugs. Thus phosphoproteomics can also be used as a powerful tool in personalized medicine. Currently, phosphoproteomics research has made great progress in the study of kidney diseases, largely promoting the study of changes in various hormones and cytokines in kidney functions and diseases. An example is in the study on the effects of vasopressin on renal collecting duct cells [59-60]. There is also a report on renal tubular epithelial cell function and epithelial-mesenchymal transition, induced by angiotensin II and transforming growth factor-β (TGF-β) [61-62]. In addition, Gonzales *et al* [63] have found that the phosphorylation sites of serine-811 in NaCl cotransporter (NCC)[R2] is a potential biological target for renal disease and that another phosphorylation site of serine-256 in AQP2 can be used to assess the activity of vasopressin and then monitoring the process of disease [64].

Glycoproteomics

Glycoproteomics is a branch of proteomics that identifies, catalogs, and characterizes those proteins containing carbohydrates as a post-translational modification [65]. Glycosylation, which exists in over 50% proteins, is recognized as an important post-translational modification [66]. Protein glyco-sylation is involved in a variety of biological processes of cellular immunity, cell adhesion, regulation of protein translation, protein degradation, and so on. The contents of glycoproteomics research include the identification of glycoproteins, elucidation of glycosylation sites, and analysis of the structure and function of proteins. Currently, the common research technologies of glycoproteomics include the separation and enrichment of glycoproteins and glycopeptides [67-68], mass spectrometric analysis of protein glycosylation sites [69], real-time and high-throughput analysis on carbohydrate chains [70], and the structural and functional analysis of glycoproteins.

Certain glycosylations may change during the process of tumor development, which may help makeearly diagnosis of cancers and monitor the disease progression. Furthermore, research on the altered glycosylation of proteins during tumor development may reveal the regulation mechanism of the tumor cell at the molecular level. Glycoproteomics is now widely studied for the identification of biomarkers for the diagnosis of cancer and other diseases, such cancers of breast [71], lung [72], stomach [73], and ovarian cancer [74], liver fibrosis [75], and Alzheimer disease [76].

Chemoproteomics

Chemoproteomics uses a chemistry-based approach to characterize protein structure and functions. In general, functional small molecules are often used to interfere with certain aspects of the proteome, and target proteins may be detected and isolated due to chemical-protein interactions. Different from common approaches in qualitative or quantitative proteomics, chemoproteomics focuses on the chemical-protein interactionsand provides a possible new technology for target discovery [77], which is considered as a promising function-based proteomics [78].

The most common chemoproteomics research process is as follows: first, protein extracts are incubated with a chemical probe or small molecule chemicals. Then, the proteins are separated using affinity chromatography and identified by high resolution MS. Finally, further bioinformatics analysis is conducted to characterize the protein structure and functions [79]. The process usually involves several approaches, including activity-based protein profiling (ABPP) [80], compound-centric chemical proteomics (CCCP) [81-82], protein chip or protein microarray [83], and network analysis [84].

Chemoproteomics is a kind of function-based proteomics and is increasingly applied in several fields of drug target discovery and validation. In the study of target discovery, for example, it has been successfully used to recognize targets to block the *Plasmodium* invasion of red blood cells. Cysteine proteases are necessary enzymes for *Plasmodium falciparum* to survive. In their study, Greenbaum *et al* [85] prepared chemical probes targeted to cysteine protease, and found falcipain 1 to be cysteine proteolysis active, and then YA29.eps was screened from database as a falcipain inhibitor. As an-

other example, in 2010, CHEN Zhu developed chemoproteomics-based approaches to elucidate the mechanism of acute promyelocytic leukemia (APL) being treated by arsenic trioxide and concluded that oncoprotein PML-RAR is a direct drug target of APL [86].

Metabolomics

The term "metabolome" refers to the complete set of small-molecule metabolites to be found within a biological sample, such as a single organism. Metabolomics is defined as "the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification" [87]. The approach was pioneered by Jeremy Nicholson at Imperial College London. Nuclear magnetic resonance (NMR), LC/MS, and GC/MS are the most common technologies in metabolomics research. The data generated in metabolomics usually consist of measurements performed on subjects under various conditions; these measurements may be digitized spectra, or a list of metabolite levels. Several pattern recognition methods and statistical programs are currently available for analysis of both NMR and MS data, such as principal components analysis (PCA) and partial least squares (PLS) [88]. Comprehensive software XCMS, freely available since 2006 to analyze global MS-based metabolomics datasets has been developed at The Scripps Research Institute [89-90]. Other popular metabolomics programs for mass spectral analysis include MZmine [91], MetAlign [92], and MathDAMP [93].

Any disturbance on living systems, regardless of physiological, pathological, or other factors, will cause changes in the metabolites. Therefore the metabolome represents the physiological or pathological status of organisms. Metabolomics thus can be used in toxicology [94], disease diagnosis [95-96], molecular pathology [97], and a number of other fields.

Pharmacometabolomics

The term "pharmacometabolomics" was first proposed by Clayton in 2006 [98]. From the changes in metabolome for an individual patient caused by drug administration, pharmacometabolomics may describe a detailed mapping of drug effects on certain metabolic pathways implicated in the mechanisms of variation of response to treatment. Such metabolic profiles represent a complete overview of individual metabolite or pathway alterations, providing a more realistic depiction of disease phenotypes. This approach can be applied to the prediction of response to a pharmaceutical compound by patients with a particular metabolic profile.

Personalized medicine is a very important application field for pharmacometabolomics. Prior to drug administration, the metabolic phenotype of individual patients is studied and employed in a predictive manner to determine the potential responses of therapeutic agents. In 2006, Clayton [98] applied ^{1}H NMR-based metabolomics to study an acetaminophen-induced liver toxicity model. For the first time, it was demonstrated that an individual's response to a drug can be predicted by their metabolome, and that there is an association between the pre-dose urinary composition and the extent of liver damage sustained after paracetamol administration. In our group, a metabolomic approach was proposed to assess the feasibility of chemosensitivity prediction in a mouse xenograft model of human gastric cancer. Based on the data of metabolic profiles and k-Nearest Neighbor algorithm, a prediction model for chemosensitivity was developed, and an average accuracy of 90.4% was achieved, suggesting that pharmacometabolomics can be used for chemosensitivity prediction in the treatment of cancer [99]. Besides personalized medicine, pharmacometabolomics is also a powerful tool for research on drug toxicity assessment [100-101], efficacy evaluation [102], and mechanisms of action [103].

Lipidomics

Lipids are the structural components of cell membranes, serving as energy storage sources and also participating in many important cellular functions. It has been proven clinically that many critical diseases are associated with lipid metabolism disorders, such as Alzheimer's disease, diabetes, and some infectious diseases. Studies have shown that mammalian cells contain 1 000 to 2 000 kinds of lipids. In 2003, Han *et al* proposed the concept of lipidomics [104]. The lipidome is the complete lipid profile within a cell, tissue, or organism, and is a subset of the metabolome. Lipidomics is the large-scale study of pathways and networks of cellular lipids in biological systems [104-106]. Although it is often considered as a branch of the more general "metabolomics", lipidomics itself is a distinct discipline due to the uniqueness and functional specificity of lipids relative to other metabolites.

Lipidomics analysis is based on multi-dimensional LC/MS, and mainly includes the following steps: lipid extraction, lipid separation, lipid detection, lipid identification, quantification, and data processing. Lipids are often extracted by acid, alkali, or a neutral solvent with traditional procedures established by Bligh/Dyer and Floch [107]. The simplest method of lipid separation is the use of thin layer chromatography (TLC), while it has limited sensitivity; thus solid-phase extraction (SPE) and LC are extensively used. Lipid detection is often by using electrospray ionization or matrix-assisted laser desorption/ionization (MALDI). Mass spectrometric identification of lipids is mainly through qualitative analysis and comparative MS^n analysis to a reference substance. Further development of the quantitative analysis of lipids is based on isotope labeling. Finally, bioinformatics is used to process the qualitative and quantitative results.

Lipidomics can determine the key lipids and enzymes which may suggest potential abnormal pathways or pathogenic mechanisms, and thus an effective manner for diagnosis and treatment may be developed. In recent years, lipidomics has been increasingly studied, especially in the field of discovery of lipid indicators for diagnosis [108], drug targets [109], and pharmacological mechanisms [110].

Other omics technologies

Phenomics

Phenomics is the study concerned with the measurement of phenome as changes occur in response to genetic mutation and environmental influences. In 1996 Garan first proposed the

concept at the University of Waterloo in a speech. Phenotype refers to the entire physical and biochemical traits of organisms, including skin color, eye color, weight, and specific individual characteristics. The phenotypes in phenomena are generally affected by genetic or environmental factors, while the phenotypic differences between individuals may be due to environmental or genetic variation, such as single nucleotide polymorphism resistance (SNPs). Phenomics has come to be used to bridge the genotype and phenotype of the organism.

The research on phenomics is mainly performed on a phenotype-microarray platform which enables one to monitor simultaneously the phenotypic reaction of cells to environmental challenges observed on microliter plates. In 2006, Niculescu and his colleagues proposed PhenoChipping as a quantitative method for phenomics analysis. Phenomics has been mainly used to study genotype-phenotype relationships [111], genetic basis of complex traits [112], and crop improvement [113].

Immunomics

Immunomics studies the response and regulation process of the immune system on pathogens, which deals with all immune-related molecules, together with their targets and functions. Immunomics includes the techniques of genomics, proteomics, and bioinformatics. On the basis of genomics and proteomics research, immunomics makes full use of bioinformatics, bio-chip, structural biology, high-throughput screening, and systems biology technologies to study the immune system and immune responses, so as to discover new susceptibility genes and new immune-related molecules. The immune system shows great diversity compared with other body systems. For such a highly complex system, traditional research methods are largely limited, while immunomics may be a new powerful approach. Immunomics is now mainly applied in vaccine development [114-115], target identification [116], and disease diagnosis [117].

Metallomics

Metal elements play an important role in biology in spite of their low levels. It is estimated that one third of proteins need metal ions (usually a transition metal ion, such as copper, iron, zinc, and molybdenum) as a cofactor to perform their biological functions, and are often called "metal proteins". In 2002, Haraguchi *et al* proposed the term “metallomics” for the systematic study of metal or metalloid elements of cells, organs, or biological tissues [118]. Metallomics can be defined as the “comprehensive analysis of the entirety of metal and metalloid species within a cell or tissue type” [119], and can be considered as a branch of metabolomics, even though metals are not typically considered as metabolites. Metal elements in metallomics include the biological metals combined with biological macromolecules, such as metal proteins, metal enzymes, metal nucleic acid fragments, metal-containing ligands (organic acids, amino acids, etc.), and metal polysaccharides, and also the free alkali and alkaline earth metal ions. Metallomics aims to reveal the physiological functions and biological effects of the metallome. The key problem is associated with the structure elucidation of a biologically active metallome.

As the most commonly used approaches, inductively-coupled plasma mass spectrometry (ICP-MS) and neutron activation analysis (NAA) enable the simultaneous quantitative analysis of multiple elements [120]. Synchrotron radiation X-ray micro-fluorescence analysis (SR-μXRF), and synchrotron radiation micro-fluorescence beam based CT, EDX, PIXE, SIMS, and LA-ICP-MS, are also used to study the distribution of the metallome [121]. Metallomics is also applied in the field of environmental evaluation [122] and in drug discovery [123-124].

Cytomics

Cytomics involves research on the structure and function of cellular systems, subsystems, and their functional components at the single cell level. Cytomics study is often based on genome databases, and also uses genomics or proteomics technologies. Sensitive, non-invasive and fluorescence-based methods are most widely employed in cytomics to conduct the integrated analysis of a single cell. The comprehensive analysis of cell morphology can be performed according to cell fluorescence quantitative data and cell imaging. Currently, the main cytomics technologies include flow cytometry, laser capture microdissection (LCM), confocal laser scanning microscopy (CLSM), laser scanning cytometry (LSC), high-content screening (HCS), and bio-imaging.

Cytomics provides strategies and effective approaches to pharmaceutical research, such as target validation [125], drug development [126], pharmacological and toxicological evaluation [127], and clinical efficacy of predictive and personalized medicine [128].

Ionomics

It is generally known that ions play a crucial role in all biological behaviors of an organism, especially in energy metabolism, enzyme activity, intracellular signaling, and transportation. In 2003, Salt and colleagues proposed, for the first time, the concept of ionomics[129]. Ionomics studies the measurement and biological processes of elementals of an organism to address biological problems. Various techniques can be used to measure the elemental composition in ionomics. The most important ones are ICP-MS, X-ray fluorescence (XRF), inductively-coupled plasma optical emission spectroscopy (ICP-OES), synchrotron-based microXRF, and neutron activation analysis (NAA) [130]. Ionomics is currently applied in functional genomics [131], modern plant nutrition [132], and other research areas.

Interactomics

The interactome is the whole set of molecular interactions in a particular cell. The term interactome was originally coined in 1999 by a group of French scientists headed by Bernard Jacq [133], and is more often described in terms of biological networks. Interactomics is a discipline at the intersection of bioinformatics and biology that

deals with studying both the interactions and the consequences of those interactions between and among proteins and other molecules within a cell [133]. Molecular interactions can occur between molecules belonging to different biochemical families or within a given family, such as molecules of proteins, nucleic acids, lipids, and carbohydrates. Interactomes may be described as biological networks, and most commonly, interactome refers to protein-protein interaction (PPI) network and protein-DNA interaction network (also called a gene-regulatory network), or subsets thereof. Therefore, a typical interactome is constructed by transcription factors, chromatin regulatory proteins, and their target genes. Interactomics aims to compare such networks of interactions between and within species in order to find how the traits of such networks are either preserved or varied. Now it has come to be used as a routine approach to predict the function of proteins of unknown functions, especially in the field of drug discovery [143, 173-175].

Application of Omics in Pharmaceutical Research

Omics still have some limitations in the application, for instance, omics data analysis may produce false positive or false negative results in view of such complicated-massive data; due to the limited sensitivity or accuracy of analytical methods, some very important functional molecules in trace level cannot be observed; moreover, results of omics research often lack enough specificity. However, it still attracts a growing number of research interests worldwide. Currently, the production of large omics data sets has become routine, and thus pharmaceutical research has entered into the new era of omics. Now, pharmaceutical research increasingly relies on genomics, transcriptomics, proteomics, and metabolomics, and even the combination of multiple omics technologies. In almost every aspect of pharmaceutical research and drug development, including target discovery, efficacy evaluation, safety assessment, mechanism research, personalized medicine, and so on, omics techniques can be used as efficient and powerful tools, as shown in Fig. 2. Omics research is the most essential part of systems biology and network biology, and makes it possible to fully understand the pathological processes of diseases, and to reveal the key pathways and possible mechanisms of pharmaceutical research and drug treatment. Moreover, omics studies may highlight the potential targets for drug development, allowing for efficient safety assessment and personal medicine. The extensive application of omics techniques in traditional Chinese medicine (TCM) and some other ethnic medicine practices in the past decades should also be noted. The characteristics of the global analysis of omics fulfil the requirements of study on the most complicated research subjects. Now, omics has come to be recognized as a powerful approach for pharmaceutical research, especially in studies of target discovery, personalized medicine, toxicology, and traditional Chinese medicine.

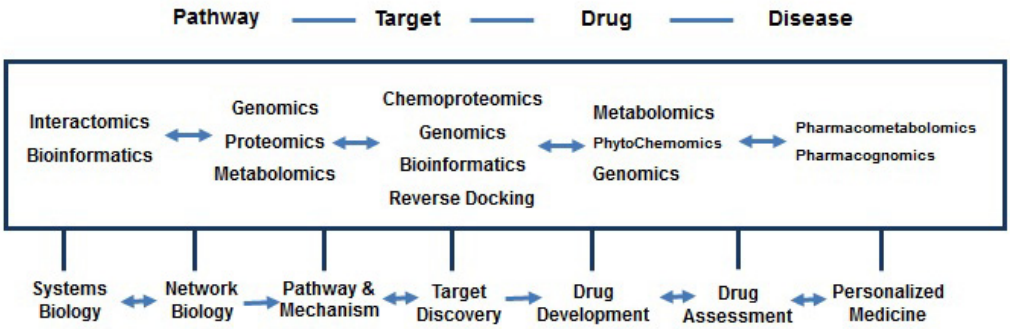

Fig. 2 Roles of omics in pharmaceutical research and drug development

Target Discovery

Target discovery plays a critical role in new drug development. In the past, drug development was largely dependent on only about five hundred known drug targets. Genomic studies indicate that humans have 30 000−40 000 genes and many more proteins, many of which are potential drug targets for human diseases. So, at least 90 percent of the target proteins have not yet been discovered. To discover and validate new drug targets is the first step in new drug development, and is also of great significance for the elucidation of the mechanisms of disease pathology and the effects of drugs.

Historically, drug development based on a single chemical and a single target is low efficient. In recent years, omics and other systems biology technologies are widely applied, and provide new ideas for target identification and new drug development. There are presently several novel omics-based technologies applied in target discovery, such as microbial genomics, differential proteomics, nuclear magnetic resonance (NMR), cell chip, RNAi, gene transfection, and gene knockout modeling. These high through-put approaches produce vast amounts of data, and with the accumulation of omics data, a series of databases have been constructed, such as OMIM (Online Mendelian Inheritance in Man), Cancer Gene Census, COSMIC, TTD (Therapeutic Target Database), DrugBank, and GEO (Gene Expression Omnibus).

Omics research and the related databases will improve the efficiency of target discovery. Based on multiple omics and associated databases, the common process of target discovery and validation is shown in Fig. 3. First, a disease model is constructed and biological samples, or, more directly, clinical samples are collected. Second, omics analyses are performed, including genomics, proteomics, metabolomics, transcriptomics, and lipidomics. Third, bioinformatics is used to process the acquired omics data, and disease-related biomarkers are proposed. Bioinformatics is also used to retrieve information from related databases, and potential target candidates or disease-related biomolecules are discovered using methods of data mining, reverse docking, and network biology. Functional analysis is then performed on these disease-related substances and the functional disease-related biomolecules are proposed as potential targets. Finally, the targets are verified by pharmacological studies at the molecular and cellular levels and subsequently in animal models.

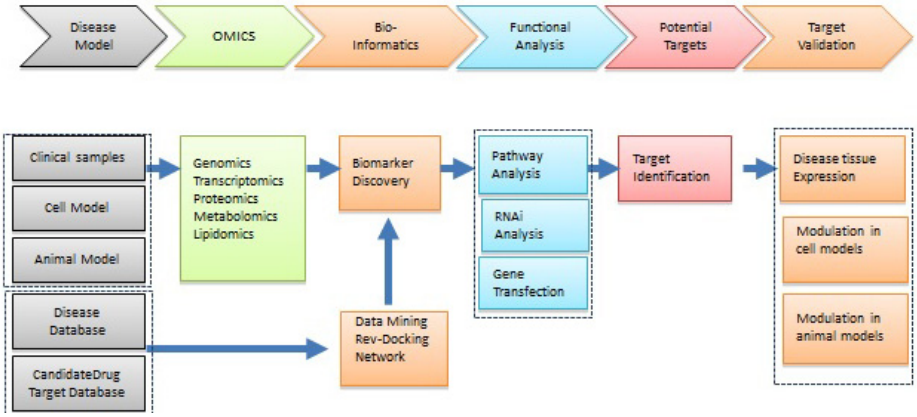

Fig. 3 Strategies of drug target discovery based on omics

Internet Databases for Target Discovery

Extensive genome databases provide the basis for drug target discovery. Since the 1990s, expressed sequence tag (EST) databases have been used in the search for new genes, such as cathepsin K and orexin receptors [134]. With the completion of the human genome project (HGP) and further genomics research in the post-genome era, vast amounts of information on genes and expressed sequence data are produced, and many related databases have been established. Some databases store information associated with disease related genes, and may be used for target discovery.

Human disease-related genes were recorded in OMIM (Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim/), LocusLink, The Human Gene Mutation and some other databases, such as COSMIC (www.sanger.ac.uk/genetics/CGP/cosmic), Cancer Gene Census (www.sanger.ac.uk/genetics/CGP/Census) [135]. GEO (Gene Expression Omnibus) is another important disease-related genes database with a wealth of cancer related microarray data. In 2003, Daniel *et al* established the ONCOMINE database (http://www. oncomine.org), which specifically collected cancer-related microarray data [136]. The database had collected 715 datasets and over 86,733 samples as of March, 2014.

Compared with disease-related genes, the number of known drug targets is much lower. TTD provides information on successfully applied targets and their treatment. The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information, where 7678 drug entries are contained, including 1555 FDA-approved small molecule drugs, 155 FDA-approved biotech (protein/peptide) drugs, 87 nutraceuticals, and over 6000 experimental drugs, and additionally, 4270 non-redundant protein (i.e. drug target/enzyme/transporter/carrier) sequences are linked to these drug entries. PDTD (Potential Drug Target Database) is a dual function database that associates an informatics database to a structural database of known and potential drug targets. PDTD is a comprehensive, web-accessible database of drug targets, and focuses on those drug targets with known 3D-structures [137]. PDTD contains 1207 entries covering 841 known and potential drug targets, with structures from the Protein Data Bank (PDB).

Gene Ontology (GO, http://www.geneontology.org) provides genetic and biological functional information for multiple species of organism. The Kyoto Encyclopedia of Genes and Genomes database (KEGG, http://www.genome. ad.jp/kegg) is a database resource for understanding high-level functions and utilities of biological systems, such as cell, organism and ecosystem, from molecular-level information, especially large-scale molecular datasets, generated by genome sequencing and other high-throughput experimental technologies. Meanwhile, there are plenty of database resources on relevant protein-protein interaction networks and biological pathways, such as DIP, Reactome, NCI (Nature Pathway Interaction Database), HPRD, and Biotarca.

Omics based target discovery

Genomics and transcriptomics have provided the earliest applications for target discovery. Microarray analysis can simultaneously screen and identify drug or disease-related genes by comparing chip data between disease groups and control groups, which may be used to predict relevant biomarkers or potential drug targets. However, it requires a complex procedure of data processing, and a lot of validation activities, and it reflects the level of mRNA expression which may not be consistent with protein expression and function. This may be a limitation for a wide application of microarrays in the fields of drug target discovery and validation. Nevertheless, there are many successful examples [138], especially in the drug target study of Alzheimer's disease [139], Parkinson's disease [140], and cancer [141].

Proteomics also can easily distinguish disease-related proteins by comparative analysis of the proteome from normal and diseased cells, and these proteins may be potential targets for drug development. Fong *et al* [142] have found that TROP2 is a potential diagnostic marker for oral squamous cell carcinoma, and is expected to be used as a target for new anti-oral squamous cell drug development. Chemoproteomics is a promising approach to specifically identify potential drug targets through protein-chemical interactions. A known small molecule drug is used as a chemical probe to capture certain proteins which are specifically bound to a probe drug. Through biological functional analysis, these proteins might be considered as potential targets for new drug development. For example, using chemoproteomics, YA29.Eps is discovered as a potential target for an anti-*Plasmodium* drug [85], and PML-RAR is found to be a target for the treatment of acute promyelocytic leukemia [86].

Interactomics is also applied to drug target discovery. In a systematic perspective, the protein in a cellular context conducts its function through interaction with other molecules, and therefore a drug may not have a single molecular target, and multiple molecular targets may be involved. Therefore, it is necessary to study drug targets and protein functions in a molecular network. Currently, the protein-protein interaction network is the most common molecular network, which involves much more complex information on the biological function of proteins. Based on omics analysis and data from related databases, disease-related networks and drug-action networks can be constructed. Comparison of domain–domain interactions and interfaces across an interactome can then guide the identification of selective drug targets or drugs targeting multiple proteins (to block parallel pathways in a network) [143]. In particular, the core nodes in both networks represent the most important molecules which are highly related to disease or drug administration, and may be considered as potential targets.

Toxicity

Drug toxicology plays a vital role in pharmaceutical research and drug development. Indeed, toxicity is one of the most common reasons for the termination of a drug development process. Drug toxicology can guide clinical medication and reduce adverse drug reactions. In the past 20 years, a series of omics technologies have been applied in toxicology, and have promoted the development of various research fields in toxicology.

Toxicogenomics

Toxicogenomics means the application of genomics in the field of toxicology. The study of toxicogenomics is to clarify the relationships between toxicity and the changes in gene expression, and then to identify potential genetic toxicants and further to understand their mechanism of action. Microarray is the most commonly used technology for toxicogenomics. It is considered that almost all toxic reactions are accompanied by changes in gene expression profiles [144]. Compared with traditional toxicity research, toxicogenomics provides a much more sensitive and comprehensive platform for drug safety assessment.

By measuring gene expression at a large-scale, the most relevant and sensitive genetic changes can be found and used as biomarkers for risk assessment. For example, the expression of genes involved in DNA damage repair may be a sign of genotoxicity [145]. Transient early changes in expressed genes may be due to a body's stress response, while long-term changes of gene profile may be related to chronic toxicity, or may merely be an adaptive response of the body. This method is very useful for determining chronic toxicity, carcinogenicity, or the secondary toxic effects of drugs. Moreover, in the early stages of new drug development, the specifically expressed, toxicant-specific gene or proteins may also be developed as biomarkers for the prediction and understanding of the potential toxicity of drugs. This is especially the case for lead compounds, which may produce a toxicity evaluation mode with high sensitivity and efficiency. This toxicity evaluation mode provides much more valuable information on the mechanism of toxicity in a relatively short time. Compared with the traditional studies, toxicogenomics brings new insights into drug toxicology.

Toxicoproteomics

Toxicoproteomics, as part of the larger field of toxicogenomics, seeks to identify critical proteins and pathways in biological systems that are affected by, and respond to, adverse chemical and environmental exposures using global protein expression technologies. Toxicoproteomics integrates three disciplinary areas of traditional toxicology, pathology, and protein differential expression analysis. Currently, this approach can reveal toxicant-reduced protein expression, and can be used to study post-translational modifications and protein-protein interactions [146].

By comparing protein expression profiles of specific cells, tissues, or organs to those induced by toxicants, toxicoproteomics may highlight in a short time a series of specifically expressed toxicity-related proteins which are likely to be the executive molecules of functional impairment caused by the

toxicant. Subsequently, through antibody analysis techniques, new toxic protein markers can be discovered. These toxic markers may be applied to study the mechanism in the human body at a safe dose. For example, Yamamoto *et al* [147] have studied the protein expression profiling in liver tissue induced by four hepatotoxic drugs (acetaminophen, amiodarone, tetracycline, and carbon tetrachloride), and the results show eight proteins, scuh as CA3, HSP60, and AK4, are significantly altered in injured liver. Hierarchical clustering analysis indicates the relationship between toxicity and the changes in protein expression, biochemical, and histopathological indicators.

Toxicometabolomics

The use of metabolomics in toxicology, "toxicometabolomics", is rapidly increasing, particularly owing to advances in MS, which is widely used in the life sciences for phenotyping disease states [148]. Generally, toxicometabolomics discovers toxicity-related biomarkers by analysis of the characteristic changes in the levels of endogenous metabolites in biological fluids, and can disclose toxicity-related biomarkers, which can be applied to evaluate toxicity and understand the toxicological processes.

Genomics, transcriptomics, and proteomics may directly or indirectly reveal the effects of a toxicant; however, they merely reflect the possibility of toxicity. In comparison, metabolites are the end products of certain biological processes, and are therefore directly related to biological reactions which already happened. Toxicometabolomics may therefore provide a more reliable scientific basis for toxicity assessment. Nicholson and colleagues [149] have made a significant contribution to toxicometabolomics. They have applied metabolomics to study drug toxicity on tissues and organs, and further to determine the potentially toxic biomarkers and investigate their possible action mechanism. Soga *et al* [150] have applied CE-TOF-MS to study serum metabolite profiles from mice dosed with acetaminophen, and found the level of ophthalmate in the serum is increased nearly five-fold, while glutathione (GSH) levels are significantly reduced. GSH is a ubiquitous intracellular antioxidant which protects mitochondria from endogenous oxidative injury, and thus can be used as a biomarker to evaluate oxidative stress damage caused by acetaminophen and other drugs.

Personalized medicine

Genetic and environmental factors and lifestyle may affect the disposition process of an organism on drugs, resulting in differences in drug response between individuals. However, clinicians typically treat a disease with the same drug dose, which may cause serious side effects. Moreover, in almost all countries around the world, the prescription of a drug is often based on a national dose medication drawn to local ethnic groups, which may not be suitable for the population of other countries, and may lead to poor efficacy, or even serious adverse reactions. Therefore, there is a need for expanding research in the area of personalized medicine. The concept of personalized medicine was firstly proposed in 1990s, when scientists of the HGP recognized the close association between individual genetic characteristics and a clinical disease phenotype. Particularly, single nucleotide polymorphisms (SNPs) are found and applied for the prediction of individual responses to a drug [151]. Personalization of medicine is a major health care challenge in 21st- century medicine, and is expected to provide patients optimized treatment [152].

Personalized medicine involves individual susceptibility predictions, diagnosis, treatment, and treatment evaluation, which emphasizes the effects on individual factors and the differences based on diagnosis and treatment. With the rapid development of high throughout-put analytical approaches in recent years, research of personalized medicine has received extensive attention. The completion of HGP and the following post-genomic era researches have significantly increased the feasibility of personalized medicine. The most important factor determining drug effects may be the genetic differences among different people, and if drug-related genes (drug-metabolizing enzymes, transporters, and receptor genes) are apparent, the clinician can establish a special dosage regimen according to the patient's genotype data, so as to improve drug efficacy and reduce toxicity, and meanwhile to reduce the suffering and economic burden of a patient. Personalized medicine is a perfect combination of pharmacogenomics and clinical pharmacy. Pharmacogenomics reveals the relationship between the patient's response to certain drugs and their genetic subtypes, which can assist clinicians in predicting drug sensitivity and other possible responses for patients, and enables the most efficacious drug to be chosen and the optimum dose to be used. So far, pharmacogenomics has been applied in the treatment of hypertension [153], asthma [154], high cholesterol [155], endocrine disorders [156], cancer [157], and other diseases. For example, Ferrari *et al* have discovered a cytoskeleton protein whose gene polymorphism is related to the incidence of hypertension, sodium sensitivity, and the antihypertensive effects of diuretics. Therefore, prior to antihypertensive therapy with diuretics, it is necessary to perform a pre-genetic test to decide whether this drug should be used [158]. There is also a study on β2-adrenergic receptor gene polymorphism and its sensitivity to β2 agonists. The results indicate that β2-adrenergic receptor gene polymorphism affects the desensitization of the β2 agonist formoterol [159].

Metabolomics reveals the integral characteristics of individual biological systems, which theoretically can provide a new technology platform to predict drug response and study personalized medicine. After administration, a drug will be metabolized by the intestinal flora or hepatic drug-metabolizing enzymes which may activate or inactivate drug metabolism. On the other hand, a drug and its metabolites will lead to changes in endogenous substances, which can be eventually observed as alterations in the constitution and relative concentration of metabolites in body fluids [160]. Clayton et al proposed the concept of pharmacometabolomics in 2006

[98], and it can be applied to predict drug-reaction phenotypes on an individual basis, prior to drug administration. Pharmacometabolomics is a powerful tool in the field of personalized medicine for understanding the mechanism of disease and the individual differences between drug responses, and to further predict individual differences in drug metabolism and toxic reactions. Clayton *et al* [98] have applied NMR-based pharmometabolomics to study acetaminophen-induced liver toxicity, demonstrating that the degree of liver damage could be predicted by metabolic profiling. Since then, there have been several studies reported on personalized medicine using pharmometabolomics [161-162]. For example, Keun *et al* [163] have used pharmometabolomics to analyze serum samples of breast cancer patients at an early stage and successfully predicted the effects of chemotherapy on body weight. Wang *et al* [99] have constructed a predictive model based on metabolomics study for chemosensitivity prediction in a human xenograft model of gastric cancer.

Traditional Chinese Medicine

Research on traditional Chinese medicine (TCM) has achieved promising progress in the areas of pharmaceutical chemistry, pharmacology, and TCM preparations. Presently, a number of single active ingredients extracted from Chinese medicinal plants are successfully developed as new drugs, such as artemisinin (anti-malarial) [164], arsenic trioxide (anti-leukemia) [165], deoxyschizandrin (anti-hepatitis) [166], and huperzine A (anti-dementia) [167]. In the past thirty years, research on TCM plants has attracted worldwide attention. However, due to the diversity of sources and the complexity of TCM, it is rather difficult to clarify the bioactive substances therein and their mechanisms of action. Systems biology is now generally accepted as a powerful technique for TCM research [168]. The systems biology technology platform is based on a series of omics technologies, providing new ideas and approaches in the field of TCM research.

Genomics provides new ideas for TCM research on target discovery, active component screening, and medicinal plant identification. Microarray analysis has the advantages of high-throughput, real-time, accuracy, and automation, and is very suitable for TCM identification. Zhang *et al* [169] have successfully used microarrays to identify five species of *Dendrobium*. Genomics can also be applied to discovery of the targets of TCM and provide an understanding of its action mechanism [170]. Zhang *et al* [171] have established an ischemic rat model and treated the rats with geniposide; 70 genes are found to be differentially expressed. Bioinformatics analysis indicates that geniposide can regulate gene expression in the brain tissue of focal cerebral ischemia in rats, providing the pharmacological mechanism of geniposide at the molecular level. Due to the large variety of TCMs and their complex composition, traditionally it is challenging to find bioactive components with definite efficacy and a clear mechanism of action. Genomics utilizes high-density chips to find new active ingredients from TCMs, which is much easier and can greatly simplify the research process. The common procedure is as follows: first, a particular disease model is constructed; second, the RNA is extracted from the model in pathological situations; third, the extracted RNA is reverse-transcribed into cDNA; then, the disease gene chip is established and verified by the detection of differentially expressed genes induced by the standard drug; finally, the chip is used to analyze the various compounds of the TCM, and the bioactive chemicals are discovered and structurally identified. The genomics based method provides some new ideas for TCM research, though it has inevitable limitation, especially synergistic effects of multi-components in TCM may be neglected. It is reported [172] that oligonucleotide microarrays are used to study the antitumor preparation of Coptis Root, eight isolated components, and its 12 600 genes. Through bioinformatics analysis, the effective components with anti-proliferative effects are finally confirmed.

Proteomics is also widely applied in TCM research for target discovery. Increasingly sophisticated protein structure databases make it possible to directly predict target proteins for TCM effective components using bioinformatics. Commonly used protein structure databases include PDB, MMDB, ISSD, CATH, and SCOP. By comparing the protein expression profiles of cell or animal tissue with that of a TCM-administered cell or animal tissue, the differentially expressed proteins may be suggested as probable targets. For instance, drug target discovery can be realized by the following procedures: (1) by comparing the proteome differences between control groups, diseased groups, and TCM treated groups, it is possible to directly find the potential target proteins; (2) virtual screening based technology (e.g., INVDOCK) may predict probable target proteins which tend to bind effective components in TCM, and then probable targets can be verified by protein-chemical interactions; (3) according to the results of comparative proteomics and related protein-protein or protein-drug interaction databases, protein interaction networks can be established, and the key protein which is expected to be a drug target candidate identified. In 2010, Yue *et al* [173-174] studied the cytotoxic mechanism of ganoderic acids D, B, F, K, and AM1 (effective components extracted from *Ganoderma lucidum*) in human cervical cancer (HeLa) cells, and found a variety of effects associated with the ganoderma acids target protein. In 2009, Wang *et al* [175] found that S-gambogic acid (an active component in *Garcinia* spp.) could inhibit the target protein stathmin 1 in the proliferation of HepG2 cells.

Metabolomics has the advantage of high-throughput and high sensitivity. In the past 20 years, metabolomics has attracted the most attention in TCM research, especially for the safety assessment, “Chinese medicine syndrome” determination, and pharmacological evaluation. The safety of TCM medicines is a worldwide concern, and metabolomics is widely applied in the study of TCM toxicity. Metabolites represent the end-point of a biological activity, so me-

tabolomics results reflect prior toxicological processes, which is real “toxicity”. A successful application on drug toxicity using metabolomics studies [176] indicates that triptolide in *Tripterygium* sp. may cause renal toxicity in rats. Recently, Li *et al* [177] conduct metabolomic analysis on herb pair Gui-Xiong (GX), which consists of Danggui (DG) and Chuanxiong (CX), to elucidate metabolic characters of hemolytic and aplastic anemia rats (HAA), and also to study the synergetic effect of herb pair. They have found that thiamine metabolism and sphingolipid metabolism are the most important pathways related to HAA, and GX play a pivotal role in treatment of HAA through down- and up-regulating the levels of the endogenous metabolites. In term of hematopoietic function, GX is the most effective as shown by the relative distance in PLS-DA score plots and relative intensity of metabolomics strategy, reflecting the synergic action between DG and CX. Their study suggests that comprehensive metabolomic approach is potentially useful for studying the action mechanisms of traditional Chinese herb pairs.

"Syndromes" is a specifically-used term in Chinese medicine, and is a relatively fuzzy concept, lacking uniform, objective, qualitative, or quantitative indicators. So far, there are no efficient approach to describing syndromes using modern language. Compared with traditional research approaches, metabolomics is generally considered as a more efficient tool to understand syndromes. For example, Li *et al* [178] have studied the syndrome of blood stasis due to qi deficit (QDBS) using metabolomics. Urine samples from QDBS rats and control rats are comparatively analyzed with ^{1}H NMR, and it is found that the metabolic profile of QDBS rats is significantly different from that of control rats. This analysis includes a series of related biomarkers, especially formate, creatinine, and citrate, which show significant changes in levels, indicating that the syndrome may be associated with these metabolites and metabolic pathways. Using a non-target metabolomics method, Wang and colleagues [179] have discovered potential biomarkers from jaundice syndrome (JS) which are also used in JS diagnosis. Multivariate data analysis methods are often utilized to identify potential biomarkers. Interestingly, forty-four marker metabolites contributing to the complete separation of JS from matched healthy controls are identified. Metabolic pathways involving alanine, aspartate, and glutamate metabolism and synthesis, and the degradation of ketones are found to be disturbed in JS patients. The study demonstrates the possibilities of metabolomics as a diagnostic tool for diseases, and provides new insight into pathophysiologic mechanistic processes.

Current Challenges and Future Directions

With the rapid development and application of high-throughput technologies and bioinformatics, omics is increasingly respected by the majority of pharmaceutical researchers. Omics techniques are widely employed in all areas of biological science, agriculture, medicine, and research fields. However, there are still great challenges in omics research, including data acquisition, multi-omics data analysis, and modeling.

First of all, how to deal with the most complicated multi-omics data sets is a great challenge. After 20 years of development, omics-based analysis has become routine, and it is no longer a problem to acquire large-scale omics data sets using high-throughput analytical approaches. In the future, in order to fully describe a biological process, the combination of multiple omics techniques will be commonly used, and produce a vast and complex data surge on various levels of DNA, RNA, SNP, protein, metabolites, and so on. Omics data is generally acquired from either experimental results or internet databases. However, the data is difficult to process due to many factors, such as the diversity of the data type, database redundancy, and lack of uniform data description standards. How to deal with such a mass amount of data, especially multi-omics data from different sources, is the most difficult challenge for omics research..

A possible efficient solution for this challenge might be network biology, which may describe biochemical systems as a network based on multi-omics data [180]. In 2004, Barabasi proposed the concept of "Network Biology" [84], which permits a better understanding of a biological system. Here, the network nodes represent the actors of intracellular processes from various perspectives (of multi-omics, including enzymes, proteins, compounds, genes, metabolites, etc.), with the edges connecting the nodes describing the relationships between these actors. Network biology relies on data mining and modeling technologies, such as database technologies, genetic algorithms, statistics, and artificial intelligence [181]. With the multi-omics databases continually expanding, some novel technologies on data analysis and processing are recently developed; for example, grid and cloud computing are applied for database services [182] and biomarker discovery [183], and Consensus Principal Component Analysis (CPCA) is proposed for multi-omics modeling [184].

How to conduct dynamic analysis is another challenge of omics research. Many researchers have come to realize that the research objects of omics, including the genome, proteome, metabolome, and lipidome, are dynamic and ever-changing, even for the same sample under the same analytical conditions. However, presently most of the omics data that are generated are “static”, ignoring its dynamic nature over time, which may cause bias in research. It is not easy to ensure enough repeatability in the discovery of omics biomarkers, and besides sampling and experimental factors, the dynamic nature of biological process maybe another important reason, which may explain the fact that many laboratory results fail to be clinically applicable.

Facing this challenge, time factors during research should be considered, and sampling at different times is necessary. It is reported that an approach using ^{35}S *in vivo* labeling analysis for dynamic proteomics (SiLAD) [185] is successfully applied to study the dynamic proteome changes in highly synchronized A549 cells, as well as in the rat liver 2/3 partial

hepatectomy surgery. Chen and colleagues [186] have presented an integrative personal omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14-month period, which can be used to interpret healthy and diseased states by connecting genomic information with additional dynamic omics activity. There is also a report [187] using time-lapse 2D-nuclear magnetic resonance based metabolic profiling for the study of the bacterial interaction between *Escherichia coli* O157 : H7 and *Bifidobacterium longum*.

The challenges also involve the requirement of promising analytical approaches. Multi-omics, especially dynamic omics, requires more advanced analytical methods. Liquid chromatography coupled with mass detection (LC/MS) is one of the most widely used, high-throughput analytical methods. Especially in the past ten years, two-dimensional liquid chromatography with high resolution mass detection (2DLC/MS) has been developed rapidly, and is much more popular in omics due to its advantage of high resolution, sensitivity, and accuracy. However, 2D separation is time-consuming, which is a significant limitation for dynamic omics. In the future, some high quality approaches of "flash analysis" are expected to be developed, which may enable researchers to rely less on the slow separation process of liquid chromatography, with possibly no separation procedure needed.

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