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'Omic' technologies: An overview

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ABSTRACT

'OMIC' technologies include proteomics, Genomics, transcriptomics and metabonomics, were touted as having the potential to revolutionize our approach to disease diagnosis, prognostication and development of novel therapeutics, to understanding the normal cellular functions, to identify the therapeutic points of intervention. Because it makes a conceptual framework for disease understanding. As the omic approach developments, further new fields will develop into branch of the biological glossary, with increasing the volumes of molecular facts added to expanding databases and by understanding the mechanism of prevention and protection against toxicity, stress and on routine development. These represent a challenging complexity for scienti?c analysis and will open new perspectives for ethno botanical and phytomedical research purposes. Thus the applications of the ''Omic'' technologies may lead to a change of paradigms towards the opening of other fields like toxicogenomics, phytogenomics etc.

KEYWORDS

Omic technology;
Proteomics;
Metabolomics;
Genomics;
Plant analysis.

INTRODUCTION

Over the last decade we have witnessed a fundamental change in how biomedical research due to the success of Human Genome Project by using the advances in 'omic' technologies[1]. There are several emerged 'omic' disciplines such as proteomics (the complete set of proteins produced in a cell), Genomics (the complete study of genes in a cell), transcriptomics (the complete set of mRNA in a cell) and metabonomics (the complete set of metabolites in an organism or cell)[1-3]. They were touted as having the potential to revolutionize our approach to disease diagnosis, prognostication and development of novel therapeutics, to understanding the normal cellular functions, to identify the therapeutic points of intervention because it makes a conceptual framework for disease understanding[1]. As the omic strategy progresses, additional new fields will become part of the biological lexicon, with increasing the volumes of molecular data added to ballooning databases and by understanding the mechanism of prevention and protection against toxicity, stress and on performance development[2,4].

Genomics and transcryptomic

The definition of genomics is not precise. The term

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was coined by Tom Roderick and originally meant analysis of the whole genome. Now it commonly refers to large-scale, high-throughput molecular analysis of multiple genes, gene products or regions of genes[5]. Transcriptomics also included under the term genomics. It explains the regulation of gene expression level in every gene or in an organism in a genome wide range[6,7]. For both the new tools are microarrays.

Microarrays in 'OMICS'

The term microarray itself, often called 'biochip', simply describes that a high number of molecules (oligonucleotides) are arranged on an extremely small space, commonly on a glass surface (up to 200.000 spots/ cm^2). The interactions of RNA or DNA extracts with these biochips are investigated and allow a simultaneous analysis of pleiotropic alterations at the genome and transcriptome level. Based on the target sequences on the glass surface, hundreds of genes can be targeted and significant changes of their mRNA can be estimated simultaneously[6].

Use of microarrays in 'Omic' technologies[8]

- Pharmacogenomics- The study of the global genetic response to drug therapies.
- Toxicogenomics- Identify profiles of gene expression associated with particular compounds or toxicities.
- Ecogenetics- The study of genetic-environmental interactions and their influence on the etiology of disease or toxic response.
- Diagnosis- Identification of malignant tissue vs benign
- Drug discovery.

Proteomics

The terms 'proteomics' and 'proteome' were introduced in 1995[9]. Proteomics is the large scale study of proteins, particularly their structures and functions. The term 'proteomics' was coined by Marc Wilkins in 1997 to make an analogy with genomics[10]. The Human Genome Project revealed that there are fewer protein-coding genes in the human genome than there are proteins in the human proteome (22,000 genes versus 400,000 proteins). This discrepancy implies that protein diversity cannot be fully characterized by gene expression analysis alone, making proteomics a useful tool for characterizing cells and tissues of interest[11]. The large-size globular structures of proteins do not allow themselves for chromatographic high-resolution separations due to the unfavorable diffusion coefficients in the separation mechanism. However, by making protein digests out of the protein samples, the task becomes easier since now we are looking at the separation of peptide mixtures[12]. This technology is mainly based on highly efficient methods of separation using two-dimensional polyacrylamide gel electrophoresis (2-DE), multidimensional HPLC, capillary electrophoresis, combinations of 1-DE gels with nano-flow micro capillary liquid chromatography and modern tools of bioinformatics in conjunction with mass spectrometry (MS)[13-17]. Affinity chromatography, fluorescence resonance energy transfer and surface plasmon resonance are used to identify protein–protein or protein–DNA interactions. X-ray tomography is used to determine the location of proteins or protein complexes in labeled cells. Further, fluorescent proteins like green fluorescent protein (GFP), yellow FP, cyan FP or red FP are frequently used to study cellular events such as localization of proteins to membranes and to cellular organelles. They can mark homogenous populations of specialized cells whose gene expression profiles should be determined by DNA microarray analysis. In fact, FPs like GFP are often used as direct transcriptional and translational reporters in living cells in a way linking transcriptomics and proteomics[18].

Metabolomics

Metabonomics (metabolomics) aims at the comprehensive and quantitative analysis of the wide arrays of metabolites in biological samples. Metabonomics has been labeled as one of the new 'omics' joining genomics, transcriptomics, and proteomics as a science employed toward the understanding of global systems biology. It has been widely applied in many research areas including drug toxicology, biomarker discovery, functional genomics, and molecular pathology etc. The comprehensive analysis of the metabonome is particularly challenging due to the diverse chemical natures of metabolites. Metabonomics investigations require special approaches for sample preparation, data-rich analytical chemical measurements, and information mining. The outputs from a metabonomics study allow sample clas-

sification, biomarker discovery, and interpretation of the reasons for classification information. This review focuses on the currently new advances in various technical platforms of metabonomics and its applications in drug discovery and development, disease biomarker identification, plant and microbe related fields[19].

Metabolic analysis can be divided into four areas: (1) target compound analysis – the quantification of specific metabolites, (2) the metabolic profiling – the quantitative and qualitative determination of a group of related compounds or of specific metabolic pathways, (3) metabolomics – the qualitative and quantitative analysis of all metabolites and (4) metabolomics fingerprinting – sample classification by rapid global analysis. The techniques used are multidisciplinary: for target compound analysis and metabolic profiling, the main techniques are gas chromatography, high-performance liquid chromatography and nuclear magnetic resonance (NMR). Further, metabolomics makes use of several complementary analytic methods; in particular, ''hyphenated'' techniques of LC/MS, LC/MS and LC/NMR are likely to have increased impact. A more detailed description of each method is given in Metabolomicsnrp (2006). These approaches rely on chromatographic separations, often coupled with well-developed calibrations for specific analytes. The metabolic fingerprinting analyses crude extracts without any separations step, using NMR, direct injection mass spectrometry (MS) or Fourier transform infrared spectroscopy[11].

Applications of 'OMIC' technologies

In systems biology

The combined information from genomics, proteomics and metabolomics will help us to obtain an integrated understanding of a cell or organism. However, these new analytic platforms are high-throughput technologies which substantially increase the dynamic range and number of metabolites and genes that can be detected[20,21]. This has created an increasing need for informatics tools to transform parallel information into real biological data and knowledge[22]. One outcome of the development of informatics tools is the advancement of systems biology. In systems biology, especially metabolomic data are presently organized with the aim to create computer models simulating biological system. Since the metabolic control analysis and functional genomics share the same agenda[23], systems biology is expected on the long term to predict both genomic activations and metabolite flows in complex systems. Their joint application is already now judged to be the ultimate phenotyping of a cell or plant and considered to have the potential to revolutionize natural product research and to advance the development of scientific based herbal medicine[22,24]. For example these technologies are likely to change and expedite the toxicological profiling of plants or drugs. In addition, the integration of these data into systems biology is expected to enable the study and understanding of living systems from a holistic perspective and to become the adequate tool to analyze complex traditional systems of medicine.

Phytomedical applications

Microarray technology has so far not been used extensively in phytomedicine and is presently in the stage of 'proof of principle'.

Determination of pharmacological activity

Wang et al. examined the effect of so-called ''herbal glycoside recipes'' on the ability of spatial learning memory in mice suffering from cerebral ischemia/reperfusion. The herbal preparations were obviously derived from the roots of Scutellaria baicalensis and Dioscorea spp. and contained baicalein (5, 6, 7-trihydroxyflavone) and dioscin (ratio 1:1). Using a cDNA microarray system containing 1176 known genes, he showed a reproducible dose dependent effect of these herbal preparations and suggested the usefulness of this methodology for elucidating the mechanism of pharmacological functions of herbal preparations[25].

To standardize the herbal extracts

A very recent report describes the analysis of two soya bean extracts. The gene expression profiles of the herbal extracts were compared with those of the single phytoestrogens. The profiles of the extracts correlated with those of the phytoestrogens, but gave quite different R-values for each phytoestrogen. Interestingly, the gene expression profiles induced by 10 mM of the phytoestrogen daidzein correlated with those derived from the total extracts (R-values: 0.73 and 0.75), but the estimated concentrations of daidzein in the extracts were much

lower. They were roughly 1/100 of 10 mM[26].

Interaction of plant components in combination

Mur et al. investigated the interaction of plant components. Salicylic acid has been proposed to antagonize jasmonic acid biosynthesis and signaling in plants. Microarray analysis demonstrated that the combination of both acted transiently synergistic on certain gene expressions (defensin and thionin, betaglucuronidase) in tobacco plants when both were applied at low concentrations, but antagonism was observed at more prolonged treatment durations or at higher concentrations. The authors concluded that there seems to be a greater sophistication in interactions than "simple" antagonism or synergism. Instead, synergistic/antagonistic mechanisms may represent positive and negative feedback loops of the same molecule combination allowing the tailoring of the plant response to a particular situation[27].

Pharmacokinetics and bioavailability of plant extracts and their combinations

Pharmacokinetic and bioavailability studies are an essential need to determine the exact pharmacological action of phytopharmaceuticals, but still unsufficient data do exist. Due to the high number of components in herbal drugs, their variable absorption and their complex biotransformation, assessments with com- plete coverage have been practically impossible to achieve by conventional methods. The new high- through put technologies facilitates these kinds of assessments and will improve the speed and yield. But again, even after the identification of the available plant components and their metabolites in plasma, functional studies are essential for determining the mode of action. This includes toxicology testing – the latter being the best developed field in the context of 'Omic'-technologies so far.

Assesment of the toxicity and safety of plant extracts

Each phytopharmaceutical needs to be assessed for safety and toxicity. Searfoss et al. identified the following general goals for the new field of Toxicogenomics equally applicable to the development of synthetic drugs and phytopharmaceuticals: a) under- stand mechanisms of toxicity 2) predict toxicity 3) develop in vivo and in vitro surrogate models and screens, and 4) develop toxicity biomarkers. These should lead to an improvement of safety, to the shortening of the drug development and a cost reduction[28-30].

In the metabonic technology

First clinical studies in the application of a metabonic strategy, utilizing high-resolution ^{1}H NMR in conjunction with chemometric methods showed that a clear differentiation of metabolite profiles before and after Chamomile tea drinking can be obtained although strong extrinsic physiological variations were observed. About 14 volunteers had ingested chamomile tea for a period of 2 weeks. Urine samples before, during and after chamomile ingestion were analyzed. Chamomile tea ingestion was shown to lead to an increased urinary excretion of hippurate and glycine with depleted creatinine concentrations. This study highlights the potential for the metabonic technology in the assessment of 'small' interventions despite a high degree of variation from genetic and environmental sources[31].

In microbial bioremediation

Microbial mediated bioremediation has a great potential to effectively restore contaminated environment, but the lack of information about factors regulating the growth and metabolism of various microbial communities in polluted environment often limits its implementation. The newly seeded omic techniques such as transcriptomics, proteomics and interactomics offer remarkable promise as tools to address longstanding questions regarding the molecular mechanisms involved in the control of mineralization pathways. During mineralization, transcript structures and their expression have been studied using high-throughput transcriptomic techniques with microarrays. Generally however, transcripts have no ability to operate any physiological response; rather, they must be translated into proteins with significant functional impact. These proteins can be identified by proteomic techniques using powerful two-dimensional polyacrylamide gel electrophoresis (2-DE). Towards the establishment of functional proteomics, the current advances in mass spectrometry (MS) and protein microarrays play a central role in the proteomics approach. Exploring the differential expression of a wide variety of proteins and screening of the entire genome for proteins that interact with particular mineralization regulatory factors would help us to gain insights into bioremediation[32].

In the molecular toxicology

In the field of molecular toxicology, the high-quality gene arrays commercially available have already allowed this technology to become a standard tool. Several national and international initiatives provided the proof-of principle tests for the application of gene expression for the study of toxicity and new existing chemical compounds[30]. In the United States, the national institute of environmental health science has created the national center for toxicogenomics to provide a reference system of genome-wide gene expression data and to develop a knowledge base of chemical effects in biological systems. Studies here showed that it is possible to identify a signature of expressed gene patterns after exposure to a given toxicant[33,34].

In the area of combination therapy

The developing 'Omic'-technologies provide us now with the possibility to detect the interaction of a drug with several targets and have indeed already demonstrated multi-target effects of single components. For example, the gene-expression profiling of α-tocopherol showed the targeting of genes related to the immune system, as well as the activation of genes related to the lipid metabolism and to inflammation interestingly with no significant change in the expression of classical antioxidant genes[35]. Similarly methotrexate (MTX) or mecaptopurin targeted a multitude of genes involved in apoptosis, mismatch repair, cell cycle control and the stress response[36]. This demonstrates convincingly that both single synthetic drugs and single natural substances can have a multitude of targets on the genetic level. Simultaneous proteomic analysis demonstrates that at least part of the genomic regulation is translated into the functional level. Thus, the 'Omic' technologies lead us away from the paradigm of 'one drug, one target and one disease'.

The reports are promising for the application of microarrays in phytoresearch and phytomedicine and they are likely to change or develop our understanding of synergy. However, the standardization of herbal extracts remains crucial. It may be simplified using those plant ingredients which show the maximum overlap in gene expression with the refined extract as shown in the example of the soja extract and daidzein[23].

Verpoorte has already hypothesized that by measuring the activity in a living organism for extracts with different composition, one may possibly identify a compound or a combination of compounds that correlate with the activity. This means that activity due to synergism and also activity of pro-drugs can be recognized[26].

It further shows that drug combinations can lead to the activation of entirely different genes than those genes activated by the individual single agents. Thus, the mode of action of the combination is, based on the gene expression, entirely different from the mode of action of the single agents. Although one may question whether the discriminating genes for the treatments are the same which are responsible for the main action of the single agent or not, the authors conclude that the method is highly suitable for the discrimination of different treatments[36].

Similarly Schulte et al., demonstrated that the combined treatment of neuroblastoma cells with cisplatin and hyperthermia lead to the up-regulation of 131 new genes which were not expressed under treatment with either cisplatin or hyperthermia alone, confirming that multimodal treatment approaches can apparently led to different effects on the level of gene expression[37].

In the cancer research

The development of high-resolution microarray-based comparative genomic hybridization (aCGH), using cDNA, bacterial artificial chromosome (BAC) and oligonucleotide probes, is providing tremendous opportunities for translational research by facilitating detailed analysis of entire cancer genomes in a single experiment. However, this technology will only fulfil its promise if studies incorporating aCGH are designed with a full understanding of its current limitations and the strategies available to circumvent them. While there have been several excellent reviews on the current status of this technology, there is currently very little guidance available regarding the appropriate design of experiments incorporating aCGH (including the strengths and weaknesses of each platform), and how best to combine the results obtained from aCGH with other 'omic' technologies, including gene expression. David SP Tan et al. present the key design issues that need to be considered in order to optimize aCGH studies, including sample selection, the definition of appropriate experimental objectives, arguments for and against the various microarray platforms that are currently available, and methods for data validation and integration[38].

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CONCLUSION

The advances in 'omics' technologies were touted as having the potential to revolutionise our approach to disease diagnosis, prognostication and development of novel therapeutics. Indeed it appears that the translational applications of genomic-based research have preceded the development of both conceptual framework for disease understanding and effective tools that can exploit the vast amounts of data derived from these efforts.

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