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PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol. 3, No.1, pp 50-57, Jan-Mar 2011

Proteomics in Computer-assisted Molecular Design

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Abstract: Computer-assisted molecular design (CAMD) also called Computer-assisted drug design (CADD) represents more recent applications of computers as tools in the drug design process. The proteome is the entire protein complement expressed by a genome, and proteomics is the study of the proteome. Proteomics is a research field that involves large scale identification, characterization and quantitation of proteins expressed in a cell, tissue, or organism under given conditions. The ultimate goal of proteomic analysis is a comprehensive and quantitative description of protein expression and quantitative description of protein expression and alterations associated with biological perturbations under a given condition. In most current applications of CADD, attempts are made to find a ligand that will interact favorably with a receptor that represents the target site. Binding of ligand to the receptor may include hydrophobic, electrostatic, and hydrogen-bonding interactions. Computational assessment of the binding affinity of enzyme inhibitors prior to synthesis is an important component of CADD paradigms.

Key words: CADD, Proteome, Ligand, Genome.

1. INTRUDUCTION

Although no single drug has been designed solely by computer techniques, the contribution of these methods to drug discovery is no longer a matter of dispute. All the world's major pharmaceutical and biotechnology companies use computational design tools. At their lowest level the contributions represent the replacement of crude mechanical models by displays of structure which are a much more accurate reflection of molecular reality, capable of demonstrating motion and solvent effects. Beyond this, theoretical calculations permit the computation of binding free energies and other relevant molecular properties.

This process extensively uses mathematical models and simulation tools based on the evaluation of potential risks from drug safety and the experimental design of new trials [1-3]. The ability to rapidly and accurately dock large numbers of candidate molecules into the binding site of a target macromolecule is a key component of lead generation in structure-based drug design [4, 5]. The most widely used computational docking method is the program DOCK [6] which has been and continues to be developed by Kuntz and his colleagues at the University of California and other scientists worldwide [6-9]. The success application of DOCK includes the in silico virtual high throughput screen for high affinity cytochrome p450cam substrates [10] and the computer-assisted design of selective imidazole inhibitors for cytochrome p450 enzymes [11]. Besides DOCK, numerous other programs have been created for virtual screening. Programs such as ADAM [12, 13], AutoDOCK [14-16], FlexX [10, 17-19], and SLIDE [20-22], and other

dock databases of compounds can score candidate molecules according to their interactions with the selected site of target protein. De novo generation of ligands can be performed with computer programs including 3D-QSAR [23-25], DISCO [26], GRID [27-30], LUDI [31-33], MCSS [27, 34], and PASSA [35]. With the rapid accumulation of biological and chemical information, CADD has been dramatically reshaping research and development pathways in drug candidate identification. On the other hand, the escalating number of therapeutic candidates is increasing demand on new technologies and strategies to streamline the process of screening for safe and effective therapies. As an emerging technology, CADD accelerates drug development by making use of the accumulated information of existing drugs and diseases, combined with inter-disciplinary inputs from other fields. In this review article, we aim to briefly summarize the recent progresses in pharmaco-proteomics and their potential application in CADD.

2. PROTEOMICS

The proteome is defined as the entirely expressed protein complement of a cell, organ or organism and it includes all isoforms and post-translational variants. The proteome is the entire protein complement expressed by a genome, and proteomics is the study of the proteome [36, 37]. Proteomics is a research field that involves largescale identification, characterization, and quantitation of proteins expressed in a cell, tissue, or organism under given conditions such as drug treatment [38-40]. Proteomic technology attempts to separate, identify and characterize a global set of proteins in an effort to provide information about protein abundance, location, modification and protein-protein interaction in a proteome of a given biological system [41, 42].

By studying the interrelationships of protein expression and modification in health and disease, or drug treatment, proteomics can be applied to biomarker discovery and drug target validation [42-44]. The ultimate goal of proteomic analysis is a comprehensive and quantitative description of protein expression and alterations associated with biological perturbations under a given condition. By studying interrelationships of protein expression and modification in health and disease or drug treatment, proteomics contributes important insights into determining the pathophysiological basis of disease [45], validating drug targets [46], and illustrating drug action [47], toxicity and side effects [48].

3. PROTEOMICS IN THE MULTI-STEP PROCESS OF DRUG DISCOVERY

Drugs exert their actions mainly by targeting functional proteins. Therefore, it appears straightforward to focus on proteins in order to investigate drug effects. Unfortunately, it is not easy to screen for protein alterations because of their high complexity. Traditional methods such as NMR analysis [49, 50] or yeast two hybrid systems [51, 52] for mapping protein-protein interactions are laborious and cannot meet the need for large scale analysis. Recently developed proteomic approaches have dramatically increased the efficiency and applicability of mapping drug-protein and protein-protein interactions. Proteomics can provide valuable information for drug discovery including target identification and validation [53, 54], lead selection [55], small-molecular screening and optimization [56, 57], and toxicity testing [58, 59]. The opportunities offered by proteomics are not limited to a list of proteins. Instead, the scope of proteomics covers the analysis of protein cellular activities and functions, including the characterization of the flow of information within the cell.

4. MAJOR TECHNOLOGICAL PLATFORMS FOR PROTEOMICS

A number of complementary technologies have been developed to analyze proteomes in a global scale. Currently, the most commonly used proteomic platforms include two-dimensional gel electrophoresis (2DE), protein chip arrays and liquid chromatography, incorporated with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF), surface enhanced laser desorption ionization time of flight (SELDI-TOF) and/or tandem mass spectrometry (MS/MS). Liquid chromatography/tandem mass spectrometry (LC-MS/MS) is an analytical method for identifying multiple components of a protein mixture [60]. The peptide mixtures in very complex protein samples are physically resolved by chromatographic separation prior to injection into the mass spectrometer to generate a more informative map, consisting of both the unique elution characteristics (column retention times) as well as *m/z* ratios of individual peptides [61]. LC-MS/MS is well-suited to examine complex protein samples, since peptides with the same nominal *m/z* are less likely to be introduced to MS/MS at the same time, and fewer artifacts arise due to ion suppression or ion-ion interference. LC-MS/MS can also overcome the difficulties of 2DE in the identification of very large and basic proteins by pre-fractionation using 1DE.

5. SUB-DISCIPLINES OF PROTEOMICS IN COMPUTER-AIDED DRUG DESIGN

There are a series of sub-disciplines of proteomic technologies, including chemical proteomics, computational proteomics, structural proteomics, and topological proteomics, are taking part drug design research fields.

5.1 Chemical Proteomics

It describes chemical nature of protein. Chemical proteomics makes use of synthetic organic chemistry, cell biology, biochemistry, and mass spectrometry to design specific protein-modifying reagents that can be used for functional studies of distinct proteins within a certain proteome [62]. The most important tool of this field is carefully designed chemical probes that can specifically target diverse sets of enzyme families. A chemical probe contains three parts, a reactive ligand that can covalently bind to the target protein/enzyme, a linker region modulating the reactivity and specificity of the reactive ligand, and a tag for identification and purification of the target protein/enzyme [62, 63].

5.2 Computational Proteomics

It is very wider and most important part. Computational proteomics refers to the large-scale generation and analysis of 3D protein structural information [64]. Accurate prediction of protein contact maps is the beginning and essential step for computational proteomics. (Table-0**1**) provide a broad range of structural and functional annotations for proteins from sequenced genomes and protein 3D structures, which make a solid foundation for computational proteomics.

5.3 Structural Proteomics

Describe structure of a protein. Structural proteomics is the determination of the relationship of all the proteins or protein complexes in a specific cellular organelle and the establishment of the relationship of these proteins in a proteome-wide scale. Combining structural biology with computational and medicinal chemistry, structural proteomics can help design drugs effectively. The major goal of structural proteomics is to determine the 3D structures of as many as possible proteins, so that other proteins in an organelle can be computationally modeled on the basis of similarity of their amino acid sequences [65, 66].

5.4 Topological Proteomics

Topological proteomics aims at localizing and characterizing entire protein networks within a single cell, providing quantitative insights into their basic organization, which are valuable information in identifying new drug targets and selecting potential lead compounds [67, 68]. The proprietary technology, Multi-Epitope-Ligan Kartographie (MELK), is an ultra-sensitive topological proteomics technology for analyzing proteins on a single cell level. MELK can trace out large scale subcellular protein patterns simultaneously within a cell, hence unravelling hierarchies of proteins related to a particular cell function or dysfunction [69]. Another topological proteomic program, TopNet, is an automated web tool designed to facilitate the analysis of interaction networks, which is available from TopNet [70] (Table-01).

Table-01: Useful Websites in Proteomics and Computer-Aided Drug Design

Websites	**Database Description**
http://www.ebi.ac.uk/dali/	Network service for comparing protein structures in 3D
http://www.rcsb.org/pdb/	Protein Data Bank
http://www.tops.leeds.ac.uk/	Topology of Protein Structure
http://www.biochem.ucl.ac.uk/bsm/PROCAT/PROCAT.html	PROCAT 3D enzyme active site templates
http://www.uhnres.utoronto.ca/proteomics/	Ontario Center for Structural Proteomics
http://cl.sdsc.edu/ce.html	Databases and Tools for 3-D Protein Structure Comparison and Alignment
http://www.protein.bio.msu.su/issd/	Integrated Sequence—Structure Database
http://scop.mrc-lmb.cam.ac.uk/scop/	Structural Classification of Proteins
http://networks.gersteinlab.org/genome	TopNet for Topological Proteomics
http://www.blueprint.org/bind/bind.php	Biolmolecular interaction network database
http://www.embl-heidelberg.de/predictprotein/predictprotein.html	Protein sequence analysis and structure prediction
http://www.ecoli-york.org/	Database for *Escherichia coli.*
http://www.genome.ad.jp/kegg/metabolism.html	Molecular interaction networks, includingmetabolic and regulatory pathways, andmolecular complexes
http://geneontology.org/	Controlled vocabulary describing molecular function, biological process, and cellular component.
http://www.broad.mit.edu/cgi-bin/cancer/datasets.cgi/	Repository of microarray data from cancer genomics publications

6. CHALLENGES IN PROTEOMIC APPROACHES

Proteomics provides a large number of validated targets for drug design and thus optimal methods have to be created to handle this challenge. This high dimensionality of data generated from these studies requires the development of advanced bioinformatics tools for efficient and accurate data analyses. For proteome profiling of a particular system or organism, a number of specialized software tools and advanced informatics are needed to support the analysis and management of these massive amounts of data. The rapidly emerging field of bioinformatics has the capacity to greatly enhance treatment efforts by serving as a bridge between proteomic raw data and applicable output [71, 72, 73]. By correlating genetic variation and potential changes in protein structure with clinical risk factors, disease presentation and differential response to treatment and drug candidates, it may be possible to obtain valuable new insights to support and guide rational decision-making, both at the clinical and public health levels. Application of this emerging integrated technology in drug development can be divided into three categories: target discovery and validation, illustration of efficacy and toxicity of compounds and identification or prediction of drug response.

7. CURRENT ACHIEVEMENTS AND APPLICATION OF PROTEOMICS IN COMPUTER AIDED DRUG DISIGN

Biomarker (Proteomic Signature) Discovery

Biomarkers are usually proteins that have their expression altered in response to a disease condition. Biomarkers can be used as signatures to determine drug efficacy and clinical effects. Since the introduction of proteomics technology, 2DE, protein chip arrays together with mass spectrometry have been extensively used in biomarker discovery. Biomarkers can provide a basis for the selection of lead candidates for clinical trials and for the understanding of candidate's pharmacology. They can also help in the characterization of the subtypes of diseases for which a therapeutic intervention is most appropriate.

7.1 Action Mechanisms of Drugs

Drugs exert their functions mainly by affecting on proteins. Therefore, it seems straightforward to focus on proteins in order to investigate the effects of drugs. Unfortunately, proteins are of very high complexity, making it much more difficult to screen for protein alterations than gene regulation. However, the efficiency and applicability of proteome analysis have been dramatically increased recently. Investigation of altered protein expression in response to drug treatment in established model systems is becoming a commonly used strategy to examine drug action mechanisms.

7.2 Molecular Drug Target

Target identification and validation are the first key steps in the drug discovery pipeline. Reliable technologies for addressing target identification and validation are the foundation of successful drug development. Proteomics has been well utilized in protein expression profiling and tissue/cell-scale target validation.

7.3 Drug Toxicity and Side Effects

Given the low success rate in drug development, detection of potential toxicity and side effects in early stages of drug candidate identification can save money and time by focusing resources on those safe drug leads and candidates. By establishing a database that defines the response of a tissue proteome to specific drugs, comparative proteomics can be used to determine the propensity for a new compound. Proteomic signatures can also be constructed based on the toxicity responses previously observed with known agents. This can provide information to screen similar compounds for modification and improvement in drug design.

7.4 Cellular Signaling Network Reconstruction

It is becoming increasingly clear that proteins perform their functions concurrently in complex networks. The rapid accumulation in genomics and proteomics information and the development of large-scale experimental techniques motivate us to develop computational approaches to dissecting different and complex signaling pathways and interactions within them.

8. CONCLUSIONS AND FUTURE PROSPECTS

Proteomic technology has progressed substantially from the simple concept of 2DE into a series of technologies capable of investigating the total protein content of a biological system and its response to changing conditions. This technology has revolutionized the way in which researchers analyze the presence and relative abundance of proteins and expedite the screening and validation process for drug discovery. Proteomics applications in drug discovery in recent years have demonstrated the potential value of proteomics in drug development. Proteomic approaches can provide valuable information for target identification and validation, lead selection, small-molecular screening and optimization.

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