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Review

Functional Proteomics : A Possible Role for Drug Discovery and Design

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ABSTRACT

The drug discovery and development process is to provide safe and effective treatments for diseases. Proteomics is an approach to life sciences research that employs a variety of technologies to characterise, study and understand the protein complement of a biological sample. The approach has been so well developed that proteomics, bioinformatics and cheminformatics are heralded as the future of pharmaceutical research. For the preliminary cognizance of this exciting technology, we describe functional proteomics, which encompasses the methodology of proteomics as a tool for drug discovery. This review highlights the methods of bioinformatics and functional proteomics of protein-protein interaction investigation and its use as a developing approach for drug discovery. Proteomics is a relatively recent concept adapted very quickly into a time and cost effective technology, which imparts a totally new orientation to medicinal chemistry and drug discovery research.

Keywords : Bioinformatics, cheminformatics, proteomics, protein-protein interaction

INTRODUCTION

Proteomics is an exciting discipline in its infancy that means different things to different people. Perhaps the most appropriate definition of proteomics is "any large scale or systematic characterisation of the proteins present in a cell, tissue, or organism." The concept behind proteomics burgeoned in the early 2000s. The approaches to proteomics generally fall into two complementary categories: methods for the global analysis of protein expression and methods for the global analysis of protein function. It is a different paradigm from conventional reductionistic scientific investigations that typically focus on a single gene or protein. [1] Most proteome approaches require access to expensive instrumentation and software. At the same time, far better methods are urgently needed to realise the full potential of proteomics and new tools are rapidly evolving.

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Unraveling the human genome will have a dramatic effect on the way drug companies discover and develop new drugs. For this reason, it is now accepted that both genomic and proteomic information will become critical to completely define the best targets for pharmaceutical research. The foremost challenge for drug discovery in the 21st century is to find new efficacious drugs to cure diseases and improve the quality of life. There is no question that to see the complete picture, it is critical to gain a perspective on drug discovery that is cell-based in addition to being focused on isolated genes or proteins. [2]

As we move into the postgenomic period, the relationship between genomics and proteomics will become apparent and exploited. Genomics is slowly but surely moving off center stage, replaced by proteomics. Though proteomics is a young field that has not fully found its stride, two new developments provide glimpses of the future.[3]

In the early 1980s, researchers proposed that sequencing the human genome would be the first step toward gaining a deeper understanding of human biology and diseases and provide new avenues for drug discovery. In the 1990s, technologies to rapidly analyse proteins and study their functions were developed. Figeys [4] discussed the different classes of protein and how they are becoming integral to drug discovery. The field of proteomics may currently be viewed as providing discovery-based tools for life sciences research [5].

FUNCTIONAL PROTEOMICS

Functional proteomics attempts to define a protein's role on the basis of the presence of specific functional groups or involvement in protein-ligand interactions, protein complexes and novel pathways. The two-hybrid approach to functional proteomics [6] is an invaluable technology for studying binary protein-protein interactions. Functional proteomics has a broad applicability across the drug discovery pipeline, from target prioritisation to extending or recycling drugs.

Proteins also interact with a range of other molecules, such as drugs, lipids and other small molecules. Chemiproteomics studies the interaction between small molecules and proteins, particularly drugs and proteins. Instead of using proteins as bait, chemiproteomics uses small molecules to "fish" for interacting proteins.[7] Protein-protein interactions play a central role in numerous processes in the cell and is one of the main fields of functional proteomics. [8]

Protein-Protein Interactions as a Target for Drugs in Proteomics

The protein-protein interaction is regulated by different environmental conditions like temperature, pH, and ionic strength, cell mechanisms by enzymes, covalent modifications, and noncovalent ligand binding. At present, protein-protein contact areas are considered to be new prospective drug targets. The numerous physiological and pathological cell processes depend on protein-protein interactions, which can be influenced by external compounds. The modern way to design new physiologically active compounds consists of three main steps: identification of a prospective target, investigation of its properties and design of a corresponding ligand.

Induction or prevention of protein-protein interaction can modify the cell reaction of designed compounds in either directions. The compounds that induce protein interaction were called dimerizers. [8] Since dimerizers must interact with two separate proteins, they consist of three parts: two anchor groups interacting with the proteins and a long linker between them.

Protein-protein interactions have a great potential as a new class of targets for novel drugs. Thus, compounds directed to the change of protein-protein interactions are the reality. Functional proteomics whose main aim is discovering such interactions may play a crucial role in finding new drug targets in future.

Functional Proteomic Investigation of Protein-Protein Interactions

Bioinformatic and functional proteomic methods allow us to predict and validate protein complexes formation. There are predictions of interacting proteins based on bioinformatic genome analysis and validation of predicted complexes with the help of the two-hybrid system, a combination of optical biosensors and mass spectrometry ("fishing").

Studying protein-protein interactions directly in human cells has tremendous advantages. The proteins are properly folded and regulated, their localisation is appropriate and the correct post-translational modifications have been made. More importantly, deciphering protein complexes, pathways and post-translational modifications provide invaluable information for understanding cellular functions and for target drug validation.

Drug companies are particularly eager to discover drug-protein interactions because the majority of drugs act directly on proteins. Although chemiproteomics is a promising new technology for discovering drug targets, technological improvements in drug immobilisation and tagging are still needed. Other approaches will undoubtedly become prominent as proteomics technology continues to evolve. Mann et al. [9] have reviewed the technologicl advances on this front.

Bioinformatics Investigation of Protein-Protein Interactions

The vast amounts of information produced by genomics and proteomics studies are generating more potential drug targets than ever before. The true complexity of cellular biology exists at the level of proteins, not genes. Furthermore, the raw genetic sequence cannot predict a protein's function, localisation, post-translational modification, or expression level in different cells. Just as automated gene and protein analysis and their database tools are pushing the genomics using rapid screening techniques, bioinformatics is going to be absolutely essential to understand cellular functions at the molecular level. Translating these targets into successful drug candidates still represents a huge challenge and the number of new drugs reaching the market is failing to show a corresponding increase. One powerful approach to converting target information into new therapeutic entities involves the use of diverse compound libraries. [10]

A major post-genomic scientific and technological pursuit is to describe the functions performed by the proteins encoded by the genome. One strategy is to first identify the protein-protein interactions in a proteome, then determine pathways and overall structure

relating these interactions, and finally to statistically infer functional roles of individual proteins. In the meantime, bioinformatics approaches may help bridge the information gap required for inference of protein function. Bock and Gough, [11,12] who had previously described data mining approach to prediction of protein-protein interactions, extended it to interaction mining on a proteome-wide scale.

Information about genes and the molecules they interact with can be used to rationally identify, design, create, and test new drugs.[13] Pharmaceutical research companies are hungry for new genome data and new bioinformatics tools that can lead to discovery of genes.

The most challenging bioinformatics problems in pharmaceutical research are identical to those faced by academic researchers:predicting protein structure from amino acid sequence, identifying regulatory interactions between genes and identifying distant homologues both across species and across families of related proteins. The Genome Project is creating a similar revolution in the way researchers think about drug research and discovery.

DATABASES OVER THE WEB

To improve access to and analysis of the database, application service providers are needed. One early proteomics database is the SWISS-PROT catalogued primary sequence information. The group's other compendia, such as SWISS-2DPAGE included data from 2D electrophoresis gels of specific proteomes, the complement of proteins in a given cell type under a given set of conditions. In recent years, as the tools for proteomics studies have improved, several new databases [14] have been compiled, each addressing a particular niche.

A pioneer company is in the process of merging computational technologies with biology, chemistry and medicine to enhance drug discovery and development. The availability of the database over the web will make it more accessible to life science researchers worldwide.

The design of a large-scale library of transcript-specific inhibiting molecules is to be synthesised by a leading company and to be used for evaluation of gene function and target validation. RNA interface (RNAi) is a biological phenomenon that involves the silencing or "knockdown" of genes in a sequence specific manner. RNAi is currently being used as a potent tool for evaluation of gene function and target validation. Any leading company is entitled to use the RNAi platform for its internal research and own the derived results.

Another leading worldwide service provider of bioinformatics solutions to the life science industry has an innovative product portfolio comprising high quality analysis and data mining tools for 1D and 2D electrophoresis gels and microarrays, the core technologies of genomics and proteomics. 2D-gel electrophoresis is a cornerstone technology, used widely in the field of proteomics.

CONCLUSION

Proteomics is now considered one of the most recent important developments in medicinal chemistry. The first decade of the 21st century is a great time to be pursuing biomedical

research due to the exciting and virtually unlimited potential of proteomics. The study of proteins and their functions might bridge the gap between drug discovery and human genomic information.

We have unprecedented opportunities to unlock the mysteries of biological processes and to develop new diagnostics and therapeutics for human diseases using global and targeted proteomic approaches. Studies on functional proteomics is timely and may contribute to the discovery of new drugs that can benefit mankind.

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