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Biomarker Discovery and Drug Development: A Proteomics Approach

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A new era of proteomics has dawned owing to the completion and annotation of the human genome and new refinements in the techniques to study proteins on the large scale. Researchers all over the world are applying proteomics to gain a better understanding of disease pathogenesis, to discover new and reliable biomarkers for early detection of diseases and to accelerate drug development.

The dynamic nature of the proteome of cells (diseased) provides ample information for studying a disease at protein level, but to gather all the information from a cell requires implementation of multiple strategies and technologies [1]. Two traditionally used techniques in proteomics are two dimensional polyacrylamide gel electrophoresis (2-DE) and mass spectrometry (MS). Many improvements have been made in these techniques to make them more effective and informative. Moreover, other advanced non-gel-based techniques like protein chip technology, phage display, activity based assays, two hybrid assays, isotope coded affinity tagging are being used in disease proteomics.

Some recently developed strategies for classical proteome analysis are isotope coded affinity tagging (ICAT) and multidimensional protein identification technique (MudPIT). ICAT categorize and quantify all the proteins in the proteome. It is a very sensitive technique with high throughput. MudPIT is another method for classical proteome study. It is the liquid chromatography/mass spectrometry (LC/MS) method which can be directly applied on crude samples. Functional analysis of proteome involves protein arrays, phage display methods and two-hybrid systems. These techniques quantify proteins and also help in determining protein-protein interactions. Some of them form bridge between classical and functional approach, like activity based probes which analyze the active protein component of proteomes [2].

Proteomics is being extensively used to study molecular basis of various diseases and development of novel drugs with better understanding of targets. Substantial interest has been generated in identifying disease biomarkers. It is a molecule that indicates changes in the physiology of a cell under diseased state and hence can be used as a diagnostic tool, therapy guidance and prognosis monitoring of diseases [3]. Cancer biomarkers are a good example which is not only help in diagnosis of disease but also helps in determining different stages of cancer, studying therapy response and verification of clinical end points [4]. Impressive data can be collected by comparative analysis of disease tissue and its normal counterpart to identify protein with aberrant expression. The sera of the patients can also be screened for auto-antibodies against tumor antigens. Immune response against tumor cells in patients with cancer is being increasingly reported resulting in production of auto-antibodies against various intracellular and surface antigens. Identification of these antigens might help in cancer screening, diagnosis and immunotherapy against the disease. Lung cancer has been extensively studied using proteomic approach. Cytokeratin isoforms were reported to correlate with patient survival and oncoprotein 18 over expression was associated with poor differentiation status in lung carcinoma [5,6]. Another type of cancer that has been studied is bladder tumor, including transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Researchers have also concentrated on identification of biomarkers of breast cancer, ovarian cancer and colon cancer. A new technology, differential in-gel electrophoresis (DIGE), combined with LC/MS, has been claimed to be a powerful proteomic procedure for the molecular characterization of tumor develpoment and for the detection of tumor-specific biomarkers in esophageal scans cell cancer [7]. Moreover, proteome analysis has also been reported to provide insights into cardiovascular diseases, inflammatory and immune diseases like rheumatoid arthritis and hepatitis.

Proteomics play an important role in drug development. All major pharmaceutical companies are implementing proteomic programs. As majority of drugs act by targeting proteins or they are protein themselves, proteomics along with bioinformatics can meet the needs of pharmaceutical industry in identifying new targets to understand insight of drug action. Bioinformatics is a tool that interprets biological information using computer-aided data. It offers algorithms for gene and protein identification, structure and function relationship predictions and functional interactions among proteins [8-10]. Information technology enables mining of DNA and protein sequence databases for similarities, screening of active compounds *in silico* by virtual screening and docking of analyses. Informatics enables easy optimization of leads in drug design, and the selection of pre-clinical candidates [9]. Growth in computing power and systematic databases has made such automated analyses possible [11].

Proteomic profiling technologies are evolving in a way to emphasize the need of increased sensitivity and high throughput. No technology can provide all the necessary information, so concurrent refinement of a number of techniques will be required for generation and interpretation of data necessary for understanding of processes involved in cell function and regulation. Thus, proteomics, particularly applied to drug discovery and disease proteomics, is evolving toward an increasingly interdisciplinary hunt that combines aspects of biology, chemistry, engineering and information science. Further improvements in these technologies will continue to drive the pursuit for better diagnostics and effective drug candidates.

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