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Proteomic Approaches for Profiling Cancer Signaling Pathways

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Introduction

After human genome is decoded, the characterization of the proteins is the next challenging task. Unlike genomic studies where individual changes may not have functional significance, protein expression is closely aligned with cellular function and activity. The proteomic profiling of functionally important regulatory proteins in cancer cells may shed light on the understanding of the molecular mechanisms of cancer development, progression and metastasis. Uncovering the underlying protein signaling network changes in cancer aids in understanding the molecular mechanism of carcinogenesis and identifies the characteristic signaling network signatures unique for different cancers and specific cancer subtypes. The identified signatures can be used for cancer diagnosis, prognosis, and personalized treatment. During the past several decades, several proteomic approaches have been adopted to identify some signaling proteins and to help us understand their structure, function, and clinical significances in various cancers. However, there are still many obstacles to develop clinically useful cancer biomarkers, including technical challenges associated with complicated bioinformatics analysis and validating potential cancer biomarkers.

Technical Challenges

The capability of proteomics to address important research questions in the biosciences is critically dependent on the development of new and improved proteomic technologies. The limited assay sensitivity of current technology, as well as the high dynamic range of protein expression, makes proteomic research extreamely challenging.

The classical proteomics approach, which utilizes two dimensional gel electrophoresis (2D) or liquid chromatography (LC) in combination with analytical mass spectrometry (MS) techniques, presents as an important platform for the analysis and identification of proteins. A major advantage of the technique is the ability to identify unknown proteins in a complex sample. However, this technique still suffers from limitations in terms of resolution, sensitivity and reproducibility. In addition, costly instrumentation and time consumption prevent it from wide adoptation. Furthermore, this technique has a much narrow range of detection, leading to false negatives: low abundance proteins are less likely to be detected.

Protein microarray, is a rapidly evolving technology and has the potential to being used for drug discovery, biomarker identification and molecular profiling of cellular materials. Clinical applicability and potential benefits of protein microarray have already been demonstrated. Forward phase protein arrays offer convenience, but are difficult to quantify. Reverse phase proteins arrays (RPPA) and antibody arrays constitute a low-cost, sensitive, high-throughput platform for marker screening, pathophysiology studies, identification of novel targets important in cancer growth, and therapeutic monitoring. However, the wider application of the protein arrays in biomedical research is still limited, partly because of the cost of producing antibodies and the limited availability of antibodies with high specificity and affinity for the target. Additionally, the difficulties associated with preserving proteins in their biologically active conformation before analysis further limits the application of this technology as a routine proteomic strategy.

Protein Pathway Array (PPA) is an innovative, powerful tool to analyze the proteins and their phosphorylated forms with good sensitivity and specificity, compared with protein microarray. This is an immune blot-based assay and was recently developed and validated in the authors' laboratory. The PPA analysis allows identifying the important, but low abundance proteins and phosphor proteins in various cancer samples. These proteins are functionally linked to angiogenesis, apoptosis, cell cycle regulation, DNA repair, migration, proliferation, signaling, stem cell association and transcription activity. In recent years, using this proteomic approach, we and others have identified various cancer biomarkers for diagnosis and prognosis and as therapeutic targets.

Bioinformatics Challenges

The identification of biomarker in proteomic data is challenging since basic statistical analysis methods fail to capture the entire signal in the data, and good protein signatures comprise not only the most differentially expressed molecules. The analysis of complex proteomes usually requires several steps from raw data processing, quantitative algorithms, statistical analysis of quantitative data, database-dependent searches, statistical evaluation of the search results, and signaling network analysis. Currently, a bioinformatic method specifically designed for protein expression array analysis is limited. However, some statistical tools developed for genomic microarray can be used for protein arrays. Examples of statistical tools that can be used for protein arrays are: BRB-Array Tools, Significance Analysis of Microarrays (SAM), Prediction Analysis of Microarrays (PAM), Signaling network construction (Bayesian network analysis, Ingenuity Pathway Analysis and KEGG pathway analysis). But, diverse statistical and bioinformatics approaches may induce different biomarker identification. Therefore, progress in proteomics research relies on well-designed and widely adopted standards for how data is produced, managed, and analyzed. Standardized analyses may ultimately lead to a better understanding of cancer, earlier diagnoses and true personalized medicine.

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Validating Cancer Biomarker Challenges

The most important contribution of proteomics cancer research has been to develop diagnostic, prognostic and predictive signatures. Unfortunately, many signatures have failed to validate by other methods or in new cohorts of patients. Several factors may contribute to these problems, including: (1) diverse patients and heterogeneous tumors, (2) an insufficient number of samples, (3) poorly experimental design, (4) different proteomics platform, and (5) diverse statistical and bioinformatics approaches.

Summary

Significant progress has been made in proteomic technology development in the last decade and this has enabled researchers to move forward to a better understanding of the disease. Some have been translated into the clinic as tools for early disease diagnosis, prognosis, and individualized treatment and response monitoring. Despite these successes, many challenges remain: proteomics platforms have limited assay sensitivity; optimal and standardized bioinformatics analysis and successful validation require complex workflows are accumulating at a rapid pace.