International Journal of Advances in Medicine
Sharma VK et al. Int J Adv Med. 2019 Dec;6(6):1953-1960
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20195259

Review Article

Current applications of proteomics: a key and novel approach

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Received: 11 September 2019
Revised: 16 September 2019
Accepted: 10 October 2019

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ABSTRACT

Proteomics represented vital applications of technologies in the identification and quantification of high to moderate proteins (cellular signalling networks) found in biological matrix such as tissues, cells and fluids. Proteomics based technical knowledge is applied and verified in several preclinical research settings such as invention of diagnostic markers for specific disease and have shown to be increased in clinical applications. Extensive studies on proteomics resulted in detection of biomarkers that have been highly advanced in using diseases for cancer, lungs, cardiovascular, renal and neuro-regenerative and Parkinson's disease by introducing human origins for biocompatibility such as urine and serum. Advancement in the proteomic methods is conferring candidate right direction for clinical usage. In this review, recent developments and widely used proteomics approaches such as Mass Spectrometry (MS), Microarray chips are elaborately addressed and also focused merits and demerits of commonly used advanced approaches such as Selected Reaction Monitoring (SRM), Parallel Reaction Monitoring (PRM) and Data Independent Acquisition (DIA) and other used proteomics and that roles, in order to aid clinicians, were also discussed in the light of biomedical applications.

Keywords: Biomarkers, Biomedical applications, Mass Spectrometry, Microarray chips, Parallel reaction monitoring, Protein quantification

INTRODUCTION

To date, in biomedical, molecular biology and clinical applications (Medicine), a wide range of latest validation tools are used for disparating proteins on gels and detecting therapeutic target by applying lasers technology, and they have emerged as innovative, versatile science division and is referred as Proteomics. It is an analytical pattern in wide ranges to identify, measure and understand post translational concerning of protein in a tissue or cell or body fluid.[1] Proteomic approaches represented an instrumental in providing information of diseases on molecular basis, clear understanding of pathophysiology, prediction of disorders thereby conferred standardized thrust, aiming at therapeutic solutions. Proteomic tools contribute a new clarity for health risk factors and have been recognized as a novel science instead of collection of tools.[2] Proteome indicated a set of proteins generated or altered by a living organism on biological systems, responsible for functional information of genes.

Proteomics considered to be a key for detecting disease in early stage, while prevention is still possible. It has played a crucial role in prognosis, diagnosis and to examine the developing disorders. In Greek, diagnosis means "capable of recognition" whereas prognosis represents "to know in advance". To determine relevant therapeutic treatment, early diagnosis is considered to be crucial. Proteomics is instrumental in characterizing "proteome" covering expression, functional pattern and association of proteins in any form.[3] Proteomics have shown to be highly dynamic and exhibited instability with response to an external stimulus in each cell. In

identifying and to understand gene function, proteomics has shown more complexity compared to genomics.[4] Such deterioration is able to predict and measure entire transcription using Microarray chips that have been adopted for an extensive examination.

The main objectives of the proteomics include (a) to receive integrated aspects of biology by understanding entire cell protein network instead of individual protein (b) this does not indicate mere identifying protein but to understand the structure, function and to evolve 3D Map of cell to determine individual gene expression

REVIEW OF LITERATURE

The structure affinity and the role of each protein within cells and living organisms could be detected by using advanced methods of protein measures. These computational results would also be claimed to body fluids to derive information as biomarkers to help health care providers and scientists for better understanding of dynamic system such as cancer affected subjects.[5]

Therefore, in the present mini review, understanding of current applications and recent advancement in proteomics in the field of biomedical, molecular biological research and advanced, feasible and most commonly used methodology and applications covering MS, Biomarkers, Microarray chips and other latest techniques under usage have been discussed in detail by compiling published sources.

Biomarker - an application of proteomics

A biomarker basically represents a protein that closely associated with disease and acts as a disorder index to diagnose, prognosis and examine the disease changes resulting to evolve strategy for therapeutic target.[6]

Basic methods used in Biomarkers in clinical settings, a tiny or traceable quantity of substances are injected into the organisms to track and to know the interaction and function in health-related risks.

Usually, in clinical settings, PSA (Prostate-Specific Antigen) has been used as a biomarker for cancer detection. In many cases, malignancy disease is detected at very late at the severe stage, may be due to poor awareness and remain expensive and time consuming to determine biomarker.

Table 1: Promising protein biomarkers for targeted proteomics assays in preclinical studies.

Relative diseases	Promising biomarkers	Sample tissue
Lung diseases	SAA1,SAA2	Plasma
	SAA1,SAA2	Serum
	TFPI, MDK,DPN,MMP2, TAMPI,	Tissues, serum
	CEA, CYFRA, 21-1, SSC	Plasma
	ALCAM,CDH1,MUC1,SPINT1, THBS4,SVEP1	Plasma
Non-small cell lung	Zyxin	Plasma
Colorectal	ITGA5,GPRC5A, PDGERB, TFRCC, 8orf45	Tissues
	CP, TIMP1, LRG1, PON1, SERPINA3	Plasma
	HLA-A, CFH, CD44, PTPRJ, HP, CDH5	Plasma
Prostate	AGR2	Urine
	TMPRSS2-ERG	Tissues
	CD44 antigen	Serum
Cardiovascular	LDH-B, CKMB, myoglobin, troponin I	Serum
Neurodegenerative	Ubiquitin	CSF
Parkinson	PRNP, HSPG2, MEGF8, NCAM1	Plasma
	SPP1, LPR1, CSF1R. EPHA4, TIMP1	CSF
	GSN, MSN, LSP1, SEPT6, TALDO1, TWF2, VIM	T-lymphocyte
Down syndrome	CEL, CPA1, MUC13, CLCA1, MUC5AC, HAPLN1	Amniotic fluid
	CEL, MUC13, CPA1, DPP4, MMP2	Amniotic fluid
	SAP, C1-inhibitor	Plasma
Pancreatic	Proline-hydroxylated α-fibrinogen	Plasma
	SFN, GSN, LUM, TIMP1	Plasma
Upper airway	244 NFL proteins	NLFc)
Hepatic fibrosis	A1BG, GFH, IGFALS, PROC, RBP4	Serum

Citation- Shi et al, 2016 with slight modification.

Therefore, throughput analyzing method has been developed for earlier detection. Proteomic technique often applied in identifying biomarkers, by searching a global protein profiling in blood, urine or body fluids, in order to find out disease-specific biomarkers using proteomics. The commonly used approach in identifying biomarker is found to be a 2D PAGE, that provides information on the association between normal and disease-affected proteins.[7] The classification of biomarkers categorized based on disease specificity and information was given by them.

They are categorized as diagnostic, prognostic and treatment predictive biomarkers. Similar bifurcation can also be applied to drug design.[8] Another study report estimated that 2% of human diseases evolved from gene damage, rest account for 98% attributed to the environmental factors that participating in disease development. In this context, proteomics implicates and act on identifying disease-associated protein that also participates in the development of the disease (Table 1).

However, very few identified biomarkers were validated and approved by the FDA for use in clinical trials.[9] The potential for profiling protein in biological fluids such as blood, serum, nipple aspirate and urine using proteomic tools, is possible to identify large scale species at a time and enables to find out appropriate biomarkers for cancer subject. In earlier, biomarkers were invented by adopting conventional methodology such as Enzyme Linked Immuno-sorbent Assay (ELISA), Western blotting, Gel electrophoresis whereas present scientific era has approached proteomics for biomarker detection using 2D PAGE, Mass spectrometry (MALDI), Electrospray ionization and SELDITOt. Two bottom-up proteomic techniques were employed to determine and ascertain the extracted proteins.[10]

It is noteworthy to state that the validation phase of biomarker discovery receives extensive attention as it needs clinical testing to be evaluated.[11,12] In recent literature Norman et al, reported that Aptamere, a short single strand RNA binding had specific site of target organism with maximum specificity and strong association and one of the classes of Aptamer (SOMAmer) has been shown to be very effective as biomarker tools in several diseases covering lung cancer, pulmonary tuberculosis and IPF.[13-20]

Mass Spectrometry (MS) based proteomics

To accuracy, reliability manifested for analyzing the protein sample, the Mass Spectrometry is only choice and significant proteomic tool to measure with improved ability in excess scale of protein in biological fluids. Using MS, variation of the protein in the given sample, identified based on their mass and charge (m/z).[21,22] Presently, two transforming technologies are prevalent in rapid development of protein related studies. Of these, one of the novel strategies for sequencing polypeptide using MS including ionization techniques that cover Electroscopic Ionization [ESI] and Matrix Assisted Laser Desorption (MALDI) followed by automation of liquid chromatography. By employing these techniques, we enable to measure and discover novel peptides on a range with extraordinary number of sequences per day with good femto-molar sensitivity in biological matrix. In recent, a diverse number of research problems else from expression of protein profiling to test signaling pathways and to develop disease specific biomarkers.

In this context, a specific strategy for each, a question arises and still remaining unanswered. Consequently, authors keep in mind, when considering designing a study, among existing variable measures, however, a promising application oriented and candidate result providing and routine working device can be preferred and applied.

When characterizing a protein, prior to initiate, it needs to assess and select technical determinants such as sample size (amount of sample), purity and nature of solubility of the given protein materials. In MS, intact protein sample can be measured with an accuracy within the range of 0.01% and can divide interactive ability or affinity of isolated protein can be covered. MS contributes a measure of purity at the level of <5% contaminants in protein preparation. Such factors are absolutely mandatory for preparing medicated proteins and to proceed structural analysis using Nuclear Magnetic Resonance (NMR).

The size of the protein such as 150 kDa and insoluble protein are exhibited provocative. As maximum insoluble mass disrupts in MS signaling and minimize the detection ability. Therefore, we are sure, on sequencing peptides using MS, as it determines 'N' terminus of the protein.[23] This method can also be performed to identify the proteins from splice variants and single-nucleotide polymorphism, however, to analyze entire complex biological materials using MS is dependent on 2 Dimensional Gel Electrophoresis (2DGEL) or HPLC that are relationized before operating Mass analysis.[24,25] HPLC is commonly used methodology for various Liquid Chromatography (LC-MS) and recognized as an instrumentation platform for the research.[26]

Although, both measures possess demerits and highlights, but still, we often use both in molecular and therapeutic approaches. Presently, electron capture dissociation has been recognized for an alternate complementary fragmentation technology which includes Orbitrap with a high resolution testing, adding with resolution time of flight mass spectrometer.[27,28] MS has been novel and commonly used for several biomarker investigations on respiratory diseases such as chronic obstructive pulmonary disease was reported. Acute respiratory syndrome was also detected using mass spectroscopic studies (Figure 1).[29]

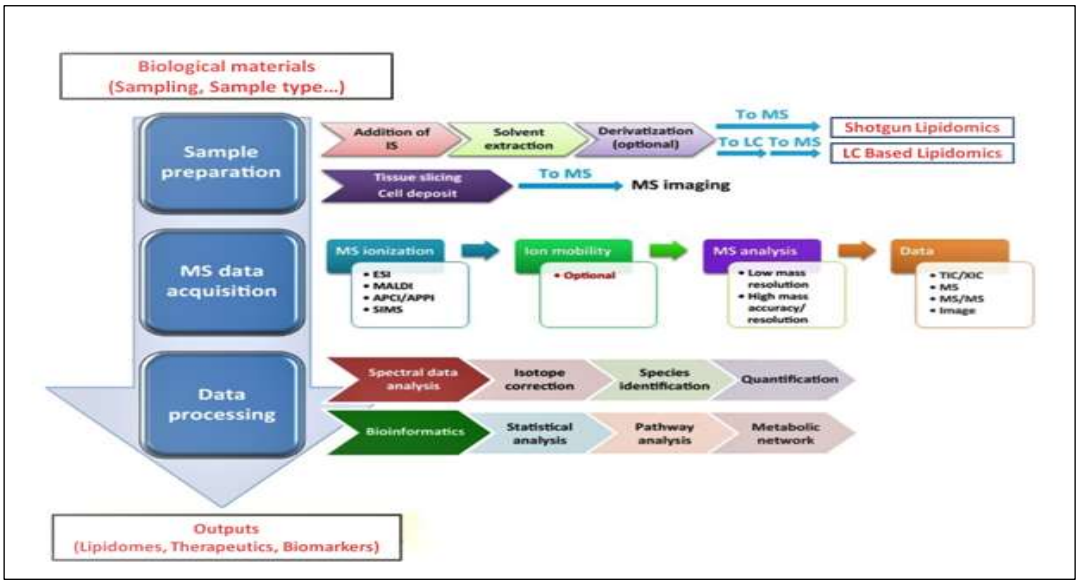

Figure 1: Basic aspects and applications of mass spectrometry.

Current trends in proteomic applications

PRM, SRM and DIA cellular signaling network

With remarkable advancement in MS instrumentation, huge number of promising biomarkers have been produced from various proteomics investigations, however, nothing has succeeded in FDA approved clinical testing which might have attributed to the scarcity of appropriate protein quantification instruments, enable to measure huge number of promising protein biomarkers (1000 human samples).[30-33] Conventional techniques such as ELISA was capable of measuring one or several protein biomarker at a time since emergence of non-antibody for corresponding new biomarker protein is limited, particularly Post Translational Modification [PTM] and variant protein. Recently, targeted proteomics grouped into three approaches (a) Selected reaction monitoring (MRM), (b) Parallel reaction monitoring (PRM) and (c) Data independent acquisition mingle with data extraction of MS/Spectra (e.g. SWATH).[34-37]

SRM is outstanding proteomic approach functioning on a triple quadrupole mass spectrometer (QqQMS).[34] This utilizes characteristics of QqQ with two level mass selection (Q1 and Q3) and showed prolonged dwell time resulting in a remarkable improvement in selectivity and higher sensitivity higher than complete scan global proteomic testing. It exhibited similar concepts as in western blotting.[38] To date, hybrid mass spectrometers with alternate of third quadrupole along with accurate mass (HR/AM), mass analyses like quadrupole-Orbitrap and (Triple- TOF) MS devices have been developed. In PRM, isolation and fragmentation of peptide precursors are resembled with SRM. PRM differ from SRM in getting a complete MS spectrum confined to each precursor in the HR/AM mass analyzer whereas in SRM transitions are monitored in low resolution quadrupole mass analyzer. Therefore, complexity of proteins can be measured in PRM with higher selectivity compared to SRM.

Although SRM and PRM were capable to quantify the proteins measured with several samples with reliable accuracy. Both have certain limitations especially in countless or multiple capacity.

The quantification can be assumed from 500 Peptides/125 proteins per SRM per time. To remove or reduce the limitations of countless ability, DIA based quantification is alternate. SWATH has been recognized as the latest novel proteome, and widely quantifying method in the field of biomedical research. This method confers and exhibited high specificity DIA for producing ion maps for complete detectable precursors. In DIA analysis, a set of wide precursors accession window are fixed to include entire m/z range of photolytic peptide. Inside the bounds, m/z windows are subjected to fragment and MS registering with high accuracy of ion spectrum, respective detectable peptides within limited elusion time and followed by elaborate data processing and clarification. Sensitivity enrichment of SRM and its usages in biomedical research can be summarized as:

SRM has been shown to be a notable method and showed more advantages than antibody based biomarkers. Protein biomarkers with SRM are closely associated with different types of cancer diseases, such as prostate, lung, colorectal, pancreatic and cardiovascular and Neurodegenerative disorders such as Parkinson's, Down syndrome and Diabetic Type 1.

Protein microarray chips

Protein microarrays referred as Protein chips that are coming under class of proteomics techniques to identify high throughput in a little quantity of sample. Protein micro assay can be grouped and bifurcated into three sections such as (a) Analytical (b) Functional and (c) Reverse-phase protein microarray. This has been instrumental in establishing protein expression examination. However, it seems to be inadequate to expose entire genome function.[39] While, MS spectroscopy was developed for different proteomic approaches to test highly sensitive protein mixture.[40] Subsequently, Edman degradation has been produced to ascertain the amino acid sequential settings for a specific protein.[41] In recent times, for quantification of protein, the methods such as Isotope-coded affinity tag (ICAT) labeling, Stable isotope labeling with amino acids (SILA) in cell culture is often used. Similarly, isobaric tag for relative and absolute quantification (iTRAQ) techniques were evolved for quantification measurements. The technique such as X-ray crystallography and nuclear magnetic resonance)/ (NMR) spectroscopy are an indicator of high throughput technique that is widely used to derive three dimensional structure of protein.

Using X-ray crystallography and NMR Spectroscopy technique a large volume of databases can be collected. Meanwhile enormous bioinformatic data are available as it stores. Several types of bioinformatic tools are developed for 3D structure prediction such as protein domain, motif testing, examining protein to protein affinity or repel followed by data analysis on MS. Alignment tools help to expose evolutionary trends of given protein.[42,43]

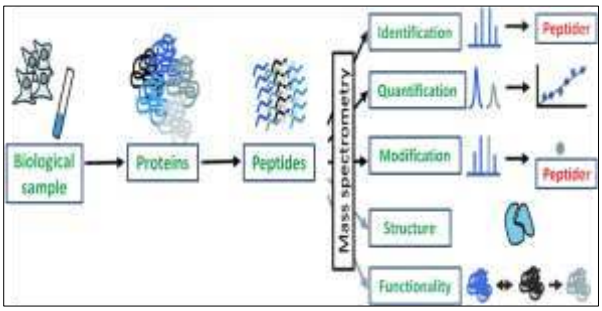

Figure 2: Structural proteomics technique.

Analytical protein microarray

This class represented by antibody microarray. Antibody microarray bestows direct protein leveling followed by antibody capture and this method is often applied to determine the expression level and interaction of protein between them.[44,45] A substantial evident that High Throughput Proteome Testing of cancer cell was practiced, using antibody microarray method to bring out varied protein expression in tissues from oral cavity of carcinoma affected patient.[46] Another study reported that this method could also be used for protein profiling of bladder cancer.[47] Inventory of cellular signaling pathways using experimental approaches were developed to characterize kinase from plant source applying protein microarray was also reported.[48]

Functional microarray

The quantity of individual protein is influenced by transcription determinants. These determinants that invade nucleus and bind with particular DNA System. This proteomic support to elucidate and stimulating enzyme action resulted powerful regulating growth process and differentiation of cells. This also helps to explain the process of ageing. Functional Micro array represented the study of several interactive patterns such as protein-DNA, RNA with protein, in between protein, affinitive with drugs, lipid and protein and enzyme substrate association as they are made of purified protein. Primary application of functional microarray was to test substrate specificity of protein kinase.[49] This functional microarray method contributes functions of huge number of proteins.

Reverse-phase protein microarray

This approach used to identify the defective and dysfunctional protein, an indicator of onset of disease. The reverse phase approach was assessed for quantification of phosphoprotein and other carcinoma disease associated protein in non-small lung cancer cell lines approaches. It examines apoptosis, DNA damage and involving various signaling pathways.[50]

Proteomic of the disease

This plays a role in capturing pathology at each stage of diseases to decide more accurate etiopathogenesis and confers information on the mechanism of diseases such as cancer, neurodegenerative diseases, inflammatory and genetic metabolic diseases. Proteomic would confer information on defective signaling pathways in cellular level was reported.[51]

Clinical proteomic

This proteomic is to achieve proteins that can be often used for diagnosis biomarkers since their expression is increased in certain physiologic and pathologic conditions such as infectious cancerous and inflammatory conditions. In case of sensitivity and specificity parameters, proteomic markers showed better option than Onome members.

Pharmacoproteomic

In clinical settings, efficiency of therapy and toxicity could be examined using protein spectrum fluctuations and their functional effects.

Gel based proteomics

Sodium Dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE)

SDS-PAGE is a sophisticated wide used resolving method in separating proteins based on their size; protein naturally potential to move towards electric field in a medium with pH with a different velocity towards the electric point. Various types of proteins in a sample of mixture move based on their mass and ratio, besides sodium Dodecyl Sulphate cleaved and denature the proteins and separate them molecular weight basis.[52]

A research group studied and reported that in African countries, Cleome spp. were consumable and possess therapeutic value for the treatment of cough, fever, asthma, rheumatism and other related diseases. An analysis of seed and leaf protein were carried out using SDS-PAGE as Brassica spp.[53] Seed Storage proteins are also isolated and identified to access genetic divergence in genotypes. Excess production of insulin is used for controlling of diabetic mellitus have characterized and purified Insulin from Camelus dromedaries.

DISCUSSION

Based on the above discussion, MS and other technologies are certainly contributed to the maximum extent in proteomics emergence, however, recent trends in the development of proteomics include, entry of worthful two targeted methods, PRM and DIA using MS quantifications. However, still needs to overcome certain limitations. SRM method is benefits in excluding required transition selection and optimization. PRM is performing and found to be promising similar effects in sensitive, countless capacity and reliability and in particular selectivity compared to SRM. Eventually, PRM showed a challenging in quantification in measurements.[12,54]

As a result, it is the eleventh hour to design an effective tool with combination of scale and selectivity for excessive proteins to quantify. Disputes, DIA excreted less sensitive, low specificity than other tools (SRM and PRM), it has been used mostly for primary screening of abundant various dynamic proteins. Subsequently, SRM or PRM has been performed for measuring low abundance proteins. Discovery of protein measurements tools with cost effective, maximum limit of measuring ability will provide the right solution for clear understanding of signal transduction network in forthcoming era.[17,55]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sharma VK, Kumar R. Current applications of proteomics: a key and novel approach. Int J Adv Med 2019;6:1953-60.