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ASIA EDITION

Proteomic technology platforms investigate the systemic alterations of protein expression

08 February 2017 | News | By BioSpectrum Bureau

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Proteomics is taking key position in biology and biomedical research. How crucial is the role of proteomics research in diagnosis and treatment of major human diseases?

Most of the attention on infectious diseases of the developing world has focused on the development of rapid diagnostic tests and novel therapeutics to ensure timely treatment and improved survival rates. For over a decade now, several attempts to discover novel biomarkers in human bio-fluids such as serum, plasma and urine have been made by various research groups. Such studies have involved the use of proteomic technologies to profile host responses to infectious diseases. The high-throughput proteomic technology platforms not only investigate the systemic alterations of protein expression in response to diseases but also enable visualisation of the underlying interconnecting protein networks and signalling pathways, facilitating the discovery of unique markers of infection. One of the first attempts to unravel the proteome of the malaria parasite Plasmodium vivax from clinical samples provided new leads towards the identification of diagnostic markers, novel therapeutic targets and an enhanced understanding of malaria pathogenesis.

Similarly, analysis of serum proteome of dengue and leptospirosis patients has led to the identification of unique protein signatures and molecular targets. A comparative serum proteomic analysis of severe and non-severe malaria in search of prognostic markers using quantitative proteomics has highlighted the presence of muscular, cytoskeletal and anti-oxidant proteins in patient sera revealing extensive oxidative stress and cellular damage in severe malaria. These findings are currently being validated in a larger cohort of patients using immunoassays. The application of proteomic technologies has shown promising leads. However, early disease detection, measurement of therapeutic efficacy, prediction of disease severity and tailored patient therapy are still some distance away.

What is the current status of India in proteomics research?

Indian researchers have been a major contributor in drafting the "human proteome map" along with international teams. Currently, more than 100 research/academic institutes are involved in core proteomics research across India. In addition to this, labs training courses, e-learning proteomics courses and remote triggered proteomics programmes are organised by institutes/private companies to educate people regarding advancement in instrument, method development and data analysis. The establishment of Proteomics Society, India (PSI) has created a platform for Indian proteomics researchers to share ideas, hold research collaborations, besides conducting annual conferences and workshops.

What are some of the recent developments in this field?

The ultimate aim of proteomics is to fully identify and quantify the entire complement of genes and post-translational modifications in biological samples of interest. For the past 15 years, liquid chromatography-tandem mass spectrometry (LC-MS/MS) in data-dependent acquisition (DDA) mode has been the standard for proteomics when sampling breadth and discovery are the main objectives; multiple reaction monitoring (MRM) LC-MS/MS has been the standard for targeted proteomics when precise quantification, reproducibility, and validation are the main objectives. Recently, improvements in mass spectrometer design and bioinformatics algorithms have resulted in the rediscovery and development of another sampling method: data-independent acquisition (DIA). Currently, DIA approaches the identification breadth of DDA while achieving the reproducible quantification characteristic of MRM or its newest version, parallel reaction monitoring (PRM). DIA is still a work in progress towards the goal of sensitive, reproducible, and precise quantification without external spectral libraries. New software tools applied to DIA analysis have to deal with deconvolution of complex spectra as well as proper filtering of false positives and false negatives. However, the future outlook is positive, and various researchers are working on novel bioinformatics techniques to address these issues and increase the reproducibility, fidelity, and identification breadth of DIA.

India is playing an increasingly significant role in global proteomics research in the post-genomic era. What are your views?

Although the development of proteomics research in India was rather slow at the outset, the last decade or so has seen a dramatic expansion in the proteomics community. The most important application of proteomics is believed to be discovery of disease biomarkers and drug targets which can lead to designing of products aimed at diagnosis and treatment of diseases like cancer, cardiovascular diseases, obesity and type 2 diabetes. A lot of laboratories in India are focussing deeply into proteomic research in the area of human biology, agriculture, disease diagnosis, animal sciences including fisheries. India has taken a lead to advance proteomic research in collaboration with world communities for which Proteomic Society of India is playing a big role.

What do you think the future holds for this field?

Proteomics research has a promising future in the coming times. Till date genome sequencing projects have resulted in annotation of genes from hundred of species of bacteria, in euaryotes (human, plants, bovine etc.). However, abinitio method of genome annotation may lead to mistakes. Therefore, proteomics can be used to validate genome annotation which has been suitably termed as proteogenomics. Biomarker discovery is a major field of research in which proteomics is playing a major role. Therefore, proteomics has a big role to play in biomarker discovery in the areas of biology including diseases diagnosis and prediction, stress tolerance in plants, reproduction and production biomarkers in animals etc.

Do you think India is still a long way off from successful translation of promising laboratory findings into practical applications? If yes, what can be the solution?

The proteomics approach has taken centre stage in biology research. However, scientists are yet to fully explore its clinical relevance. These efforts are not enough for the benefit of the huge Indian patient population. Despite some success stories, India is still some distance away from successful translation of laboratory findings into clinical practice. India needs focused, sustained policies to promote translational research through specialised mega projects. Establishment of tissue repositories or registries is the need of the hour. The country's overall healthcare infrastructure and medical informatics system also needs both public and private sector support on a long-term basis so as to facilitate more effective translation studies. Tie-ups with commercial companies to facilitate technological developments will be necessary. At present, most of the proteomic investigations are arising from individual labs in research institutes of national repute. Almost all the studies are in the discovery phase. Collaboration between scientists and clinicians will facilitate the execution of well-designed multi-institutional and multi-centric studies aimed at addressing the relevant health problems unique to India, evaluating disease outcomes and their validity.

What are some of the remarkable achievements by India in this field?

The Council of Scientific and Industrial Research (CSIR) initiated and supported a multi institutional project on "New targets and biomarkers for cancer using Genomics and Proteomics" involving the Centre for Cellular and Molecular Biology (CCMB, Hyderabad); Tata Memorial Centre-ACTREC, Navi Mumbai; Indian Institute of Science (IISc), Bengaluru, and Satya Sai Institute of Medical Sciences, Bengaluru in 2001-2002. Proteomics research in India started at the CCMB with the use of conventional two-dimensional electrophoresis (2-DE) and MALDI-TOF MS with a focus on cancer biomarker discovery in brain tumour and with ACTREC on oral cancer. In 2002, not-for-profit private organisation IOB set the standard for the upcoming proteomics facilities with high resolution mass spectrometry. In addition to contributor in human proteome map, IOB in collaboration with Pandey Laboratory at Johns Hopkins Medical Institute include the development of Human Protein Reference Database (HPRD) and Human Proteinpedia. IOB also created Plasma Proteome Database (PPD) in association with HUPO. In addition, IOB developed NetPath-a database of human signalling pathways, Pancreatic Cancer Database (PCD) and Resource for Asian Primary Immunodeficiency Diseases (RAPID) and also lead in proteogenomic analysis. The curated database of proteins associated with cervix cancer-CCDB, a database of anticancer peptides and proteins called CancerPPD, and a database of hemolytic and non-hemolytic peptides-Hemolytik have been developed by IMTECH, Chandigarh. Researchers at IISc, Bengaluru have developed quite a few protein databases related to structure and function of protein kinases like 'KinG', NrichD, PALI, PRODOC and MulPSSM. A number of protein databases such as PepBind, Immune Epitope Prediction Database & Tools, SEDB, Clostridium-DT(DB), and VPDB have originated from the Centre of Bioinformatics in Pondicherry University.

Indian researchers implement the proteomics approaches to elucidate biological mechanisms as well as to discover biomarkers for various diseases. Considerable efforts have been made to explore the mechanism of disease pathogenesis using animal models as well as cell biology and molecular biology techniques. Proteomics is employed as a study tool in tuberculosis which affects a large population in the country and is of major concern. Research institutes like National JALMA Institute for Leprosy & Other Mycobacterial Diseases, Agra and National Institute for Research in Tuberculosis, Chennai are the frontrunners in this area. The underlying objective is to characterise the various strains, decoding drug resistance and identifying biomarker candidates along with new therapeutic targets. Several studies have also been conducted on clinical isolates of wild type and drug resistant varieties of Leishmania across different institutes of the country like NCCS, Pune; JNU, New Delhi; CDRI, Lucknow; IOB, Bengaluru; AIIMS, New Delhi; NIPER, Mohali; BHU, Varanasi and IICB, Kolkata. Substantial research activities on some other immune disorders, cardiac problems, cancer, reproductive and haematological disorders have also been carried out in centres like Bose Institute, Kolkata; PGIMER, Chandigarh; IOB, Bengaluru; CDRI, Lucknow; IGIB, New Delhi and AIIMS, New Delhi using high throughput proteomic techniques. A group from Indian Council of Agricultural Research has developed FISHPROT (Fish proteomics database) with the major objectives being bio-monitoring of ecosystem biomarkers, processing of bioactive proteins/substance for pharmaceutical usage and physiological responses of fish in various ecosystems. Also major initiative on farm animal proteomics has been going on at ICAR_National Dairy Research Institute, Karnal, Haryana.

Kindly tell us something about your current research?

Extensive studies have been conducted to understand the lactation biology in bovine with special reference to milk yield and lactation persistency in farm animals. Substantial research activities have been carried out in ICAR-NDRI to gain the knowledge on physiological changes in bovine during pregnancy by implementing high throughput proteomics approaches. These studies have revealed potential protein biomarkers which can have application in early pregnancy diagnosis. Mastitis, the inflammation of mammary gland is an ongoing problem in lactating cows. Identification of potential biomarkers for subclinical mastitis is an area of active research.

--Kalyani Sharma