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A Review of Application of Proteomicsin the World's Biggest Killer Diseases and Some Foods

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***Abstract*—The proteome is defined as all the proteins expressed by the genome, an organism or a cell type. Proteomics is the study of the proteome of a cell line, tissue or organism with the aim of integrating the search for biological processes. The term proteomics refers to a wide range of studies related to the isolation of proteins from a single sample and the comparison of protein expression profiles in different samples. The knowledge of proteomics identifies the properties, quality and quantity of proteins. In the past years, various methods have been developed for proteomic analysis. One of the main goals in proteomic studies is to identify the desired proteins through their amino acid sequence. Whole proteome analysis is a major challenge. The most commonly used methods are two-dimensional gel electrophoresis (2DE), surface-enhanced laser desorption/ionization (SELDI), liquid chromatography-mass spectrometry (LC-MS), selective reaction monitoring (SRM), monitoring Multiplex reaction (MRM) and protein arrays The first step in the proteomic analysis is the isolation of proteins in samples. Two-dimensional gel electrophoresis is one of the most common separation methods in this field, and isoelectric focusing (IEF) in the first dimension and SDS-polyacrylamide gel electrophoresis (SDS-PAGE) in the second dimension enables the separation of proteins by charge and size. Laser ionization and release methods by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-TOF-MS) enable rapid ionization and identification of proteins and peptides. This article aims to comprehensively review proteomics in the worldof 's biggest killer diseases such as malaria, covid-19, Cancer and the some food items.**

***Index Terms*—Proteomics, Biggest killer diseases, Malaria, Covid-19, Food, Proteomics**

I. INTRODUCTION

Since proteins are the main carriers of biological information, the proteomic analysis provides a direct reflection of gene expression, although it is much more complex compared to genomics.

Broadly, proteomics is defined as the genome-scale analysis of protein abundance, structure, localization, modification, and activity. Currently, as one of the main components of systems biology, proteomics has attracted comprehensive attention in the fields of medical diagnosis, drug development, and mechanism studies [1].

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Proteomics technology is an important research tool to elucidate the differential expression of proteins in body fluids, cells, tissues, blood and peripheral urine samples. Blood and urine are the most used samples because their molecular compositions fluctuate in response to dynamic physiological and pathological conditions of the body. Fluctuations in gene expression levels can be determined by transcriptome or proteome analysis to distinguish between two biological states of the cell. Microarray chips have been developed for large-scale analysis of the entire transcriptome. However, increased mRNA synthesis cannot be directly measured by microarray [2]. Proteins are factors of biological function and their levels depend not only on the corresponding mRNA levels but also on host translational control and regulation. Therefore, proteomics is considered as the most relevant data set to describe a biological system [3]. Technically, proteomic analysis requires the combination of several technologies, i.e. protein processing and separation such as two-dimensional polyacrylamide gel electrophoresis (2DE), high-performance liquid chromatography (HPLC), mass spectrometry (MS) such as MADI-TOF- . MS, SELDI-TOF-MS, and MS/MS, isobaric labels for quantitative proteomic and bioinformatic analysis based on relative and absolute quantitation (iTRAQ-) [4]. In food production processes, proteins serve as ideal indicators for many properties related to food quality, comp,osition or source. Proteome analysis can identify novel marker proteins or peptides. The main application of the proteomic method is the analysis of changes in food quality [5], the identification of bioactive substances and compounds in functional foods and nutrients [6], the characterization of plant food proteins [7,8], molecular signaling for pathobiology and physiology [9], protein digestion sequence [10]. Identification of proteins that are allergenic [11,12,13], identification, targeted therapy, vaccine and drug development [14]. Proteome analysis provides a complete picture of the structural and functional information of the cell as well as the mechanism of the cell's response to different types of stress and drugs using single or multiple proteomics techniques. The aim of this review is to study the current progress in proteomics techniques and their applications. We describe studies that have used proteomic technologies.

II. LITERATURE REVIEW

A five-year outlook for malaria

Malaria has a profound effect on the public health and education systems, economy and social structures of many

developing countries, especially in Africa. Proteomic analysis of this deadly parasite began almost two decades ago by examining two-dimensional gel patterns of parasite proteins before and after the use of the antimalarial drug mefloquine as an indicator of natural genetic diversity in parasite populations. Such studies were limited at the time by the inability to easily identify proteins of interest in 2D gels, a situation that has changed dramatically in recent years with the completion of the genome sequencing project for P. falciparum and rapid advances in mass spectrometry techniques [15]. Recent advances in malaria proteomics depend heavily on the availability of the complete genome sequence of the parasite. It is only by comparing experimentally determined peptide mass and sequence data against the protein complement predicted from DNA sequence that such data can be fully utilized [16]. However, it is important to note that, while these protein sequence predictions are generally accurate, the majority of them have not been experimentally verified. However, even with the complete and annotated genome sequence of the 3D7 lineage, interpretation of malaria proteomics data is not straightforward. Therefore, it is easy to overlook the fact that P. falciparum is anything but a homogeneous organism. It is known that throughout the parasite population (it is estimated that there are between 1016 and 1018 parasites worldwide at any given time in humans alone [17], there is a high degree of polymorphism that affects many antigens. It affects the host's immune system. It has also been shown that parasites from different parts of the world differ significantly in the speed of genetic adaptation to a new drug challenge [18]. Initial efforts have been made to integrate transcriptome and proteome data for P. berghei and P. falciparum. In the second case, mRNA levels were measured on high-density microarrays and the abundance of their cognate proteins was estimated semi-quantitatively by the number of MS2 spectra detected in each protein. Although there was a relatively high correlation between mRNA and protein levels for each of the life cycle stages examined, significant differences were observed. These are often manifested as a delay between the peaks of mRNA transcription and protein amounts, a phenomenon most pronounced in gametocyte stages, but also observed for other stages. Thus, for example, the transcriptional activity in the merozoite is best correlated with the ring stage proteome in the following cycle. These observations provide general implications for the interpretation of transcriptome data as well as important biological insights into the possible importance of post-transcriptional control mechanisms in this parasite that affect the stability of mRNA species and the timing and control of their translation. These new applications demonstrate the expanding and exciting role that proteomics-related technologies are now playing in the search for new ways to combat the grand challenge of effective disease control that the malaria parasite still represents [19,20].

Proteomics in COVID-19

Multiple proteomic biomarker studies on covid-19, self-detection of the virus using targeted MS-based MRM, plasma/serum and urine proteomics to identify disease pathways and proteins of interest in patients with mild or severe SARS- CoV-2 has been done. In a study Shen et al, described pathway enrichment for proteins involved in platelet degranulation, immune cell activation, complement system pathway activation, and dysregulated metabolism pathways. A combined proteomic and metabolomic approach was used to support the identification of prognostic markers in the sera of 46 individuals with Covid-19 and 53 controls. A machine learning model was generated using proteomic and metabolomic measurements from a training group of 18 non-severe and 13 severe patients. The model correctly classified severe patients with an accuracy of 93.5. The predictive accuracy of the molecular signature was attributed to 22 proteins and 7 metabolites, and the panel was further validated using 10 independent patients, of which 7 were correctly classified. To further validate the predictive classifier, targeted mass spectrometry assays for 22 proteins and 7 metabolites were developed and applied to a second experimental group of 19 SARS-CoV-2 positive patients. This analysis resulted in the correct assignment of 16 of 19 patients [21]. D'Alessandro et al conducted an interesting study on 49 people, 33 of whom were SARS-CoV-2 positive. The aim was to investigate the effect of circulating levels of interleukin-6 (an index of disease severity) on protein abundance levels in serum. LC-MS/MS analysis showed that several proteins correlated with interleukin-6 levels, especially C-reactive protein. Pathway analysis performed on protein clusters in the serum of SARS-CoV-2 positive patients classified according to interleukin-6 levels, significant enrichment of protein clusters related to coagulation and complement cascades, immunoglobulins, enzymes showed antimicrobials, apolipoproteins and other carriers. The authors emphasized that the correlation between the hypercoagulable status of SARS-CoV-2-positive patients could be related to the severity of the disease as measured by IL-6 levels and suggested the use of profibrinolytic agents as a potential therapeutic strategy [22]. In a study of severe SARS-CoV-2 positive patients (n = 69) and non-severe patients (n = 11), Liu et al. showed that baseline interleukin-6 levels of patients with severe disease with peak body temperature during both had a positive relationship. Hospitalization and more advanced bilateral and interstitial abnormalities on chest computed tomography (CT) outcomes. Patients with severe disease also showed higher levels of D-dimer, erythrocyte sedimentation rate, lactate dehydrogenase, C-reactive protein, and ferritin than non-severe patients [23].

Anti-cancer agents

The antiproliferative effect of monaculin K was studied. Monaculin K is a secondary metabolite of Monascus, a fungus traditionally used in Asian countries for food fermentation (red moldy rice). Among other effects, monacolin K inhibits the proliferation of tumor cells in vitro, indicating a possible anticancer effect (a competitive inhibitor of coenzyme 3-hydroxy-3-methylglutaryl A reductase). Monaculin K proteome analysis was used to study biological pathways related to proliferation inhibition. Human colorectal adenocarcinoma (Caco-2) cells were treated with and without monaculin K, and cellular proteomes were compared using two-dimensional gel

electrophoresis, laser desorption ionization, matrix-assisted time-of-flight/time-of-flight mass spectrometry (MALDI-TOF/TOF MS) tandem mass spectrometry (MS/MS). The intensity of about 100 protein spots changed as a result of monaculin K treatment. 20 proteins among the proteins were analyzed by mass spectrometer. It was shown that monaculin K-mediated inhibition of proliferation was associated with modulated expression of anti-oxidation enzymes, cytoskeletal proteins, glycolytic enzymes and enzymes that mediate protein interactions. The identified proteins related to reactive oxygen stress, glycolytic enzymes, cytoskeletal proteins and enzymes involved in mediating interactions were shown in proteomic analysis [24]. An anti-tumor active fraction, TR35, isolated from Xinjiang Bacteri camel milk inhibited Eca109 cell proliferation and induced apoptosis. The aim of the study was to analyze the active part extracted from Xinjiang Bactrian camel curd on human cancer cells using in vitro and in vivo models of human esophageal cancer. Combined RNA-Seq and 2-DE mass spectrometry analysis was used to identify differentially expressed protein and RNA markers of apoptosis and necrosis. For 2-DE, each sample (treated and untreated) was cultured in triplicate. From each biological replicate, proteins were separated on a 2D PAGE gel from whole cell lysates. After Coomassie Brilliant Blue staining, more than 2000 spots were detected on each 2-DE gel (Mw range: 10e200 kDa, pI range: 3e10NL). A total of 55 protein spots had statistically significant differences in expression. This list was reduced to 33 protein spots with a fold change difference greater than two. Eight of these were up-regulated, 14 were down-regulated, and 11 spots were almost absent in treated cells compared to controls. A total of 14 different proteins were successfully identified after trypsin hydrolysis by mass spectrometry. TR35 contained 13 proteins and M35 contained a mixture of 9 proteins. There were eight of them in both TR35 and M35, but the frequency varied widely. The four most abundant proteins in TR35 are glycosylation-dependent cell adhesion molecule 1 (GlyCAM1, 42.8%), alpha-lactalbumin (a-LA, 15.27%), whey acidic protein (WAP, 13.36%), and peptidoglycan (recognition protein) PGLYRP1, 12.68%. In M35, the three most abundant proteinswere GlyCAM1 (81.02%), polymeric immunoglobulin receptor (pIgR, 7.73%) and a-LA (7.23%). Each of the other six proteins in M35 accounted for less than two percent. Proteins that appeared only in TR35 included WAP, Ig gamma-3 chain C, Ig lambda C chain, beta-2-microglobulin (beta(2)m) and an unidentified protein. The protein levels of neutrophil gelatinase-related lipocalin-like protein and PGLYRP1 in TR35 are 150-fold and about 23.5-fold higher than in M35 [25]. The researchers looked at luteolin, a product that transcriptionally inhibits CREB1 expression and blocks the epithelial-to-mesenchymal transition (EMT) of colorectal cancer cells. Luteolin is a common flavonoid found in various plant products such as celery, pepper, thyme and broccoli. Luteolin has antioxidant and immune system modulating properties. 366 differentially expressed proteins were identified by studying the proteomic profile of HCT-116 cells with and without luteolin. CREB1 degradation plays an important role in this process. Protein levels of CREB1 and its downstream target genes were decreased in luteolin-treated cells. Expression of CREB1 blocked the inhibitory effect of luteolin on colon cancer cells. Suppression of CREB1 expression is very important in the mechanism of action of luteolin inhibiting EMT of colorectal cancer cells [26].

Food-Borne Pathogenic And Spoilage Bacteria

In one study, bacterial strains from a laboratory trainee collection of pathogenic and spoilage species transmitted from seafood were studied using laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). *Acinetobacter, Aeromonas, Bacillus, Carnobacterium, Citrobacter, Clostridium, Enterobacter, Hafnia, Klebsiella, Listeria, Morganella, Pantoea, Photobacterium, Proteus, Providencia, Pseudomonas, Raveltella, Serratia, Staphylococcus, Steulococcus, Serratia, Staphylococcus, Stevanella, Serratia, Steulococcus, Sterolococcus* were selected. The two sample preparation protocols were to analyze bacterial cells suspended in an organic solvent or to analyze the sample directly. With another method of sample preparation, the cell extract was obtained from whole bacterial cells with the step of dissolution and centrifugation. The first method of sample analysis was based on the direct application of bacterial biomass from cultures to a MALDI-TOF MS plate. In the second method of sample preparation, bacterial colonies were harvested in a solvent to obtain a cell suspension of bacterial cells, and in the third method, cell suspensions were centrifuged according to the second method and the spectra were compared with the resulting spectra. of cell suspensions without a centrifugation step. Analysis of cell extracts by MALDI-TOF MS was used to create a mass library of major spoilage and potentially pathogenic bacteria in fish and seafood, which has been shown to be a rapid method for the differentiation of microbial species and It is also for classification of different types. strains isolated from seafood [27]. Pathogenic bacteria that contaminate seafood are the main cause of food poisoning and seafood spoilage. In one study, major spoilage of seafood and pathogenic Gram-positive bacteria, including *Bacillus* spp., *Listeria* spp., *Clostridium* spp., *Staphylococcus* spp. and *Carnobacterium* spp. was gathered. The strains belonged to 20 different species that were obtained from culture collections and were studied using matrix-assisted laser desorption ionization mass spectrometry (MALDI-TOF MS). A reference library, including fingerprints of 32 reference strains and extracted lists with 10-30 peak masses, was collected. Genus-specific as well as species-specific peak masses were assigned for rapid identification of bacteria and serve as biomarkers. In addition, the peak mass lists were clustered with the SPECLUST web program to show the phyloproteomic relationships between these strains. Thus, the isolated strains were clearly identified as *B. licheniformis* (1Pesc), *B. megaterium* (RPesc), *B. subtilis* (Proc6a), *C. maltaromaticum* (Proc3T4, Proc4T4) and *S. aureus* (Proc1010). The spectral profiles were very similar to the corresponding reference spectra, which allowed rapid classification of the isolated strains by simple visual comparison. When analyzing the peak mass lists, a number of common peaks with the corresponding lists of reference strains were found. As previously described for reference

strains, spectral differences between strains of the same species were also observed when comparing isolates with reference strains. Spectral profiles were significantly different in Gram-positive strains. Thus, for the genera *Clostridium* and *Listeria*, a greater number of peaks can be detected over the entire mass range, while the spectra of *Carnobacterium* and *Staphylococcus* show only 10-15 peaks. In addition, the genus *Bacillus* and *Staphylococcus* did not show any similarity at the genus level. Furthermore, when clustering the peak mass lists, species of the same genus were not grouped together. Through this method, six strains isolated from seafood were identified compared to the reference library. Phylogenetic analysis was performed based on the 16S rRNA gene with a proteomic approach [28].

Food Poisoning Bacteria

Secreted metabolites, such as extracellular proteins, have significant commercial relevance to the biotechnology and food processing industry as sources of biocatalysts. However, they also have a pathogenic potential [29]. The production of extracellular enzymes used in the food industry is mostly carried out by Aspergilli [30], but these products can also cause allergies in sensitive individuals. Identification of 28 cell surface, 102 secreted and 139 intracellular proteins based on 10 different Aspergillus proteomics studies [31] provided the status of the proteome profile in the fungal genus Aspergillus. Filamentous fungi have extremely strong cell walls [32], which makes them difficult to lyse for proteomics sample preparation for complete extraction of intracellular proteins. To analyze the samples using mass spectrometry and gel electrophoresis techniques, different methods were proposed to separate the samples and enrich them with proteins secreted from filamentous fungi culture [33]. By testing four different methods of fungal lysis using *Aspergillus oryzae*, the researchers found that mechanical lysis was more effective for the fungi used. Therefore, the identification of proteins and small molecules produced by an as yet unknown pathogen will be the first step towards the diagnosis and prevention of more foodborne diseases. The formation of biogenic amines in foods is due to the decarboxylation of certain free amino acids by the action of extracellular decarboxylases released by some amine-producing bacteria. Among these amines, histamine is the most biologically important in terms of its toxic effect. Consumption of fish and other foods that contain bacteria with histidine decarboxylase activity causes histamine poisoning. Specific mass spectral fingerprints of 16 major enteric and marine biogenic amine-producing bacteria were obtained by MALDI-TOF MS analysis to inhibit histamine formation. The histamine-producing bacteria considered in this research were obtained from international culture collections *A. hydrophila* ATCC 7966, *C. freundii* ATCC 8090, *E. aerogenes* ATCC 13048, *E. cloacae* ATCC 13047, *H. alvei* ATCC 9760, *K. pneumoniae* ATCC 10031, *Lactobacillus sp*. 30A ATCC 33222, *M. morganii* BM 65, *P. damselae* ATCC 33539, *P. phosphoreum* CECT 4172, *P. vulgaris* ATCC 9484, *P. mirabilis* ATCC 14153, *R. planticola* ATCC 33531, *S. xylosus* ATCC 29971, *S. maltophilia* 25MC6, *S. maltophilia* 15MF. The biogenic amine-producing species are *E. aerogenes* ATCC 13048, *E. cloacae* ATCC 13047, *K. pneumoniae* ATCC 10031, *R. planticola* ATCC 33531 and *C. freundii* ATCC 13048, *H. alvei* ATCC 9760, *M. morganii* BM 65, *P. vulgaris* ATCC 9484 and *P. mirabilis* ATCC 1415. Non-enteric biogenic amine-producing Gram-negative bacteria species are *P. damselae* ATCC 33539, *P. phosphoreum* CECT 4172, *A. hydrophila* ATCC 7966, *S. maltophilia* 25MC6 and *S. maltophilia* 15MF. With this method, common peaks in specific bacterial groups were identified. Therefore, two protein peaks were observed in all Enterobacteriaceae species except *Morganellamorgani*. Classification based on MALDI-TOF MS showed good correlation with phylogenetic analysis based on 16S rRNA gene sequence and confirmed the ability of the MALDI-TOF technique to establish relationships between species and microbial species [34].

Honey And Royal Jelly

The aim of a work is to propose new tools, based on molecular markers, for honey authentication. Polymerase chain reaction allowing the detection of *A. cerana* DNA in novel species primers designed to target the tRNAleu-cox2 intergenic region. A new real-time PCR method with high-resolution analysis was developed to target the 16S rRNA gene of both honey bee species, allowing their differentiation into different clusters.Bee DNA identification of Asian and European honey samples was successfully used in authentication [35].To see if available plant proteins allow proteotyping of these different species, honeys from chestnut, acacia, sunflower, eucalyptus and orange were analyzed for their proteome content.All visible bands in the SDS-PAGE profile of each honey were digested and identified by mass spectrometry on an LTQ-XL instrument, so total protein content was low. Of the total proteins identified (eight, but only seven major components of all honey types), five of them belonged to the royal jelly major protein type and were also the most abundant in all honey types.The honey proteome appears to be similar to that of royal jelly, except that its protein concentration is three to four times lower compared to royal jelly [36]. Royal jelly contains many substances including protein. In one study, royal jelly protein was determined by molecular forms of MRJPs by HPLC, SDS-PAGE, 2-DE and MALDI TOF/TOF with size exclusion.First, RJ proteins were extracted by centrifugation methods. RJ proteins were generally separated into five peaks (640 kDa, 280 kDa, 100 kDa, 72 kDa and 4.5 kDa) by size exclusion HPLC.The two main peaks were 280 kDa and 72 kDa.The 280 kDa protein was separated by SDS-PAGE into a 55 kDa band.It was also separated into several points from pH 4.2 to 6.5 by 2-DE.These spots were identified by MALDI TOF/TOF MS as MRJP 1, thus, MRJP 1 is an oligomeric complex linked by non-covalent bonds, and another protein, a peak of 72 kDa in HPLC, was identified as MRJP 2 [37]. Two-dimensional gel electrophoresis proteome strategies combined with high-performance liquid chromatography-chip/electrospray ionization mass spectrometry and bioinformatics were used to identify royal jelly PTMs.Phosphorylation and apolipoprotein III-like protein were identified for the first time in MRJP 1, MRJP 2, and a

new site was localized in the precursor of venom protein 2.Methylation is the most important PTM of MRJP, causing MRJP 1-5 polymorphism in the RJ proteome.Therefore, the biological role of PTMs and RJ for human health was deciphered [38].

III. CONCLUSION

In prior years, extraordinary useful advances have been made in the field of proteomics. The technologies are rapid, sensitive and provide greater proteome coverage. In addition, a combination of these technologies has achieved success in the purification, analysis, characterization, quantification, sequence and structural analysis, and bioinformatic analysis of a large number of proteins in all types of eukaryotic and prokaryotic organisms. Proteomic analysis of human disease is advancing rapidly. Application of its findings will improve our understanding of the role of individual proteins or entire cellular pathways in the initiation and development of disease. Proteomics tools are a promising alternative to classical food analysis methods due to their sensitivity, high throughput, multiplexing, robustness and discrimination power, which shows that they will play an important role in food authenticity and food adulteration detection. An exciting challenge will be to integrate data from genomic analysis and differential, functional and structural studies of proteins and cross-reference them to biological processes occurring in diseases. The development of these databases will accelerate the analysis of clinical samples with high efficiency and cost-effectiveness, so that early detection, prognostic, diagnostic and therapeutic tests and strategies will be available to physicians and ultimately to patients. Accordingly, more work is still needed to improve the reproducibility and performance of popular proteomics tools.

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