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Review Article

Proteomics as an Indicator for the Research of Cell Apoptosis in Toxicology

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Abstract

Apoptosis is the major form of programmed cell death and is essential for tissue homeostasis in organisms. It not only plays important roles in cell development and immune system, but is also associated with several diseases. With the process of signal transduction, protein expression is an important indictor in apoptosis. To analysis the characteristic of biochemical events, proteomics--the simultaneous analysis and quantification of protein abundance widely used in cellular morphology and death, is applied.

This review article highlights a series of new researches from the realm of proteomics crosses the field of toxicology to support that proteomics has been applied in verifying apoptosis pathway, exploiting diagnosis biomarker, evaluating drug therapeutic doses, biomarkers finding, and clinical disease management. As a holistic measure of cell apoptosis, proteomics will continue to make great strides as an indicator for the toxicology research.

Proteomic technologies are still facing a number of challenges, such as removing impurities, acquiring low abundance proteins, discovering clinical and multi-omics technology, limit the popularization and application in toxicology. However, with innovation in technology, proteomic is still going to have a promising foreground.

Keywords: Proteomics; Proteome; Toxicology; Apoptosis; Biomarker

Introduction and Background

Apoptosis is the major form of programmed cell death and is essential for tissue homeostasis is in organisms [1]. It not only plays important roles in cell development and immune system, but is also associated with several diseases [2]. Many pharmacological and physiological mediators are able to modulate it. A huge array of toxicants may either accidentally activate the process or produce toxicity by disturbing physiological cell death patterns [3]. Proteins are the star actors within the cell, carrying out the duties specified by the information encoded in genes. They are also the main components of the physiological metabolic pathways of cells [4]. The death signals may lead to render cell dysfunctional and complete cell death, while protein as the receptor and functional expression subject is the critical indictor in apoptosis.

In the new period, omics analysis has become a trend with more comprehensive and extensive understanding. As taken place in toxicology, changes of paradigm have become the pure function driven biosciences to systematic and holistic approaches. The term proteomics is coined in 1997, following the successful genomics projects and the classic protein chemistry evolved into a high throughput and systematic science [5-6]. The goal of proteomics is a comprehensive, quantitative description of protein expression. Through the passion of scientists interested in understanding molecular mechanism, including disease processing, proteomics has emerged as an important tool in the study of apoptotic cells and how different therapeutics affects the status of a cell [7-8]. Nowadays, many applications of proteomics are applied in the research of toxicology or other relative areas. These instruments and techniques not only facilitate protein separation and identification, but also provide information about protein networks [9]. What's more, they enhance the level of human understanding for the bioprocess. Table 1 shows a summary of the features of different methods or techniques, and their application in various samples, more technically sophisticated, give advances in research. With its rapid evolution in the past ten years, the proteomic methodology has been applied in the field of toxicology, verifying apoptosis pathway, exploiting diagnosis biomarker, evaluating drug therapeutic doses, finding biomarkers and managing clinical diseases. Apopto Proteomics database development, multiple omics profiling technologies, proteins separation and proteins identification methods still needs to be improved. However, there is no doubt that proteomics will make a great impact on toxicology.

Regulation of apoptosis

Apoptosis, also known as programmed cell death, is the energy-dependent process of cell death [10], accompany by cellular or extracellular protein expression. Apoptosis plays important roles in physiology and pathology, and can be triggered by numerous stimuli [11]. Proteomics-- the simultaneous analysis and quantification of protein abundance, is used to analyze the characteristic of biochemical events, resulting in changes in cellular morphology and death [12]. It is applied in exogenous stimulate toxicology, verifying the apoptosis pathway for diagnosis biomarker and drug development, integrating miRNA, mRNA and proteomic profiling approaches toxicology to identify the biological pathways both *in vivo* and *in vitro* systems, and revealing the regulation of apoptosis.

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Table 1: Technologies of proteomic research in toxicology.

TECHNOLOGIES OF PROTEOMIC RESEARCH IN TOXICOLOGY				
Methods	**Principles**	**Applications**	**Advantages**	**Disadvantages**
Proteins Separation				
Two-dimensional gel electrophoresis (2-DE)	Molecular Weight (MW); Isoelectric point (pl)	Far-ranging cell samples	Visualization Distinguish phosphorylation; Relative low cost	Difficult to detect low abundance proteins; Difficult to detect hydrophobic and strongly acid basic proteins; Time comusing
Differences gel electrophoresis (2-DIGE)	Molecular Weight (MW); Isoelectric point (pl) Cydye Fluorescent tags	Small amount of samples than 2-DE; Micro cutting samples	The heightened accuracy; Eliminate the differences between the glue	Can only detect denatured proteins
Liquid Chromatography (LC)	Chromatography	A single protein or simple sample separation; Membrane protein; Low abundance proteins;	High throughput; Automation analysis; Fast speed and high sensitivity	Hardly detect complex mixture of proteins; More cost
Isobaric tags for relative and absolute quantitation (iTARQ)	Isotope-coded covalent tags	Membrane proteins; Nucleoprotein; Extracellular protein; Low abundance proteins; Strong basic proteins	High flux; Proteome dynamic monitoring of multiple time points; Quantitative sensitivity; Low sample amount	No visual spot detection; more cost
Proteins identification				
Matrix-Assisted Laser Desorption/ Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS)	Gasification and ionization of peptides; Soft ionization Utilize m/z value	Single sample point	High Sensitivity; High accuracy; High resolution	Dependence of high proteins purity
Surface-Enhanced Laser Desorption/Ionization Time of Flight Mass Spectrometry (SELDI-TOF-MS)	Chip technology; Gasification and ionization of peptides; Soft ionization	Complex samples; Serum; Urine; Clinical Specimens	Protein purification unnecessary; Informative; High Sensitivity; Relation with protein-protein interaction	Bad repetitiveness
Electro spray Ionization Mass Spectrometry	Coulomb force between the positive charge; Different m/z value	Unstable proteins	More soft ionization than MALDI; Integrated Ion; High sensitivity; High degree of automation	Expensive; High apparatus requirement

As a naturally occurring mycotoxin and food contaminant, Ochratoxin A (OTA) has various toxicological effects, especially nephrotoxicity, as an inducer focusing on proteomic approaches. An iTRAQ-based mitoproteomics approach is used to explore possible toxicity mechanisms of OTA and potential protective regulations of N-acetyl-L-cysteine (NAC) using the mitochondria of Human Embryonic Kidney 293 (HEK 293) cells. The significantly different proteins are mainly involved in the perturbation of the mitochondrial electron transport chain, inhibition of protein synthesis, and induction of stress response and cell death. NAC can almost completely reverse the adverse effects of OTA at the protein level to protect cell death. Using the data of proteomics, a hypothetical model of OTA-induced mitochondria damage is proposed to provide a framework for the toxicity mechanism [13]. To further reveal the mechanism of cytotoxicity, an iTRAQ-based quantitative proteomics approach is used in identifying differentially expressed proteins between Lon Protease 1 knock-down cells and control. Defense against oxidative stress in the mitochondria, regulating protein synthesis, modification and repair, maintaining thebalance of carbohydrate metabolism, and assisting in mtDNA maintenance are realized the protective function processes through the results. Meanwhile the method of combination of RNAi and iTRAQ-based quantitative proteomics paves the way to gain a better understanding of the toxicity mechanisms [14]. OTA-induced early hepatotoxicity also been revealed by combining multi-omics methods [15]. The comprehensive understanding of toxicological effects is also conducive to the further exploration of detoxification mechanism.

Perfluorooctanoic acid (PFOA), one of the most commonly used perfluorinated compounds in commercial products, has been associated with a number of adverse health effects [16]. However, the molecular mechanisms involved in PFOA toxicity are still not well characterized. By investigating the alterations in protein profilein human nontumor hepatic cells, the proteomic study proposed that the inhibition of some proteins, including GRP78, HSP27, CTSD and hnRNPC may be involved in the activation of p53, which consequently triggers the apoptotic process [17]. This has shined a new light on the molecular mechanisms responsible for PFOA-mediated toxicity in human liver cells.

Drug-induced liver injury (DILI) is a significant clinical problem, commonly classified into intrinsic (dose-dependent and predictable) and idiosyncratic (non-dose-dependent and unpredictable) hepato toxicity [18]. A novel high-through put proteomic approach based on 2D-nano-LC–MS/MS was applied to simultaneously evaluate the alterations of global protein expression involved in the response of *levo*-tetrahydropalmatine (*l*-THP) treatment in normal human liver cells. Further analysis by Western-blot confirmed that mTOR and MEK2 proteins express at lower levels comparing with control, and provide detail evidence to support that *l*-THP is capable of inducing apoptosis in mammalian liver cells [10]. This is helpful to evaluate drugs in therapeutic doses.

To identify the biological pathways, proteomics lead researchers to have a deeper comprehension of the actual active players of cellular function comparing to genomics. Because mRNA is a disposable message and only a limited amount of it gets translated into proteins [20-22]. To find the regulation of apoptosis in megakaryocytes, a combined proteomic, transcriptomic and bioinformatic approach is used to elucidate the molecular mechanisms, underlying Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) signaling via

its receptor VPAC1. Comparison of genomic and proteomic data, provide novel insights into toxic mechanisms and is necessary for human health risk assessment [23]. After two-dimensional difference gel electrophoresis and tandem MS, 2384 differentially expressed genes/proteins are detected. The majority of the 120 proteins modulate by PACAP belong to the class of "cell cycle and apoptosis" proteins, and ingenuity pathway analysis further identify apoptosis as the highest scored network with NF-κB as a key-player [24]. The viewpoint NF-κB as well as p38, ERK 1/2 and JNK 1/2MAPK plays critical roles in immune response also detect by 2-DE [25], to reveal the function of protein and signals.

The molecular mechanism of the apoptosis effect of SNX-2112, a novel inhibitor of Hsp90 currently used as an anti-tumor drug, induces apoptosis inmultiple tumor cell lines is poorly understood. Combination of transcriptomics and proteomics approaches further reveal that caspase signals originate from mitochondria dysfunction, mediate by Akt signaling pathway inactivity [26]. The results from combination of transcriptomics and proteomics demonstrate the therapeutic potential of SNX-2112 against human chronic myeloid leukemia [27]. There are many examples of proteomics research playing important roles in the field of cell apoptosis.

Biomarkers finding and disease research

The cell apoptosis and dysfunctional are often occurrence and development with disease. Biomarkers are indicators of a specific biological state because of the proteomic methodology has rapidly evolved in the past ten years [28]. Proteomics and metabolomics, in combination with conventional endpoints and transcriptomics, have helped in generating mechanistic hypotheses and identifying or qualifying biomarkers. Toxicologists and pathologists are working to detect biomarkers and their applications as reliable predictors of pathological conditions, such as neurodegenerative diseases, types of cancer, chronic obstructive pulmonary disease, urinary tract obstruction, is important for clinical disease management.

A surplus of death signals is associated with neurodegenerative diseases [29] because the death signals may not only lead to complete cell death but may also render cells dysfunctional [1]. The specific diagnostic and prognostic biomarkers are helpful in managing neurodegenerative diseases. To identify relevant biomarkers and therapeutic targets for these disorders, the cerebrospinal fluid (CSF) proteome are focused on the mechanisms underlying neuronal death in neurodegenerative diseases. Compared with the secretome of apoptotic and surviving cerebellar granule neurons (CGNs), a total of 1375 proteins are identified in CGN-conditioned media by using two different heavy isotopelabels follow by liquid chromatography couple with Fourier transform tandem mass spectrometry. Among these proteins, 47 are differentially expressed in the supernatants of apoptotic and surviving neurons. It should be considered when using targeted quantitative proteomics approaches to characterize or validate CSF biomarkers of neurodegenerative disorders [30], which is a noteworthy advance in specific diagnostic.

A set of survival signals is predominantly associated with cancer. Systemic mining of cancer exoproteome/secretome has emerged as a pivotal strategy for delineation of molecular pathways with mechanistic importance in cancer development, as well as the discovery of diagnostic/prognostic biomarkers [31]. Cancer cells have the ability to evade apoptotic signals and promote survival beyond their normal life span. This is a hallmark of tumorigenesis, and proteomics analysis is often used in the area of cancer therapy and biomarker screening [32]. Pediatric as trocytomas, a leading cause of death associated with cancer, are the most common primary central nervous system tumors found in children. It progresses rapidly and invades surrounding tissues. The check sample analyze by 2D SDS-PAGE, mass spectrometry (MALDI-TOF), RT2 miRNA PCR Array System, shows that vimentin, calreticulin and 14-3-3 epsilon protein are hub proteins in these neoplasm's. The novel proteins and micro RNAs with expression changes on pediatric astrocytoma could serve as biomarkers of tumor progression [33]. This article indicate that the large-scale analyses allow a fairly accurate prediction of different cellular processes altered in tumors. Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related deaths worldwide [34]. To examine the background of lymph node metastasis (LNM) in gastric cancer, the proteomic approach is used. Members protein of the beta-3integrin (ITGB3) pathway are significantly enriched, which has not been observed before. This report suggests a novel role for the integrin pathway in the development of LNM in gastric cancer [35].

Nasopharyngeal carcinoma (NPC) is a leading lethal malignancy, especially prevalent in the Cantonese region of southern China [36]. To identify novel biomarkers for the early detection of NPC patients, 2D-DIGE combine with MALDI-TOF-MS analysis is performed to identify different protein expression in the carcinogenesis and progression of NPC, using LCM-purified normal nasopharyngeal epithelial tissues and various stages of NPC biopsies [37]. The results determine that ENO1 and CYPA are the two potential novel biomarkers for the early detection of NPC, and the combining-biomarker method what by detecting both of them makes disease diagnosismore stability and efficiency.

In developing worlds, long-term exposure to pollution irritants causes an inflammatory response in the lungs, resulting in narrowing of the small airways and breaking down of lung tissue [38]. Chronic obstructive pulmonary disease (COPD) develops as a significant and chronic inflammatory response to inhaled irritants. Chronic bacterial infections may also add to this inflammatory state [39-40]. Because of that, COPD has becoming one of the leading causes of morbidity and mortality around the world. However, the exact mechanisms of COPD and its progression are still poorly understood. There is an increasing need to be able to perform proteomic studies on patients with COPD, to describe the association with disease specificity, severity, progress and prognosis as well as monitor the efficacy of therapies. Proteomic results in 60 patients diagnosed with broncho-alveolar lavage revealed inflammatory signaling, free radical scavenging and oxidative stress response, glycolysis and gluconeogenesis pathways correlated with the COPD. The most relevant signaling link was through the NF-κB pathway [41]. Induced sputumis analyzed by cysteine-specific two-dimensional difference gel electrophoresis (2D-DIGE) coupled with mass spectrometry to identify proteins involved in COPD pathogenesis [42]. Another proteomic analysis highlights ways to identify novel biomarkers for diagnosis, therapy, and prognosis in COPD. In the results, through the detection of lung tissue, broncho-alveolar lavage, sputum and serum, surfactant protein-A (SP-A) protein may represent a helpful

biomarker in the early detection of COPD and other relate disorders. Sputum polymeric immunoglobulin receptor (PIGR) -- a glycosylated secretory component, is significantly elevated in the bronchial and alveolar epithelium to moderate COPD [43-44].

Urinary tract obstruction (UTO) is a commonly noted disorder on prenatal ultrasound that has the potential to lead to permanent loss of renal function [45]. An *in vitro* model has been developed which involves mechanical stretch of proximaltubule cells grown on flexible plates, which mimics the physiological conditions during UTO. This study employs a one dimensional SDS-PAGE fractionation procedure, following by in-gel digest and LC-MS/MS analysis in a semi-quantitative experiment, using spectral counting to relatively quantify changes in protein expression following the established model of UTO. Quantitative analysis shows 135 increased and 182 decreased expression proteins, providing a more complete characterization of changes in protein abundance as a result of stretch than previous studies, supporting a number of previously undescribed proteins in proximal tubule cells that may play a role in UTO [12]. To believe proteomics will be a bigger stage in disease prevention and control.

The integration of proteome research evidence into clinical practice is going to require extensive studies on analytical and clinical validity of biomarkers in large cohorts of patients, establishing the necessary laboratory infrastructure, education of healthcare and genetic professionals, counseling services for patients and external quality assurance testing [46-47]. It is important to the development of personalized medicine, adapting the evaluation of predictive and prognostic biomarkers, and the application of cancer-type specificdrugs that targets individuals for vanquishing diseases.

Enrich cell apoptosis databases

Omics analysis has becoming the hottest trend in technology and the dramatic impact, but this emerging science facing a massive data, it is crucial to support the development of a relative database. Various types of high-throughput-omics data become rapidly available [48], which are useful for proteomic analysis and data relevance.

For formulate proteins involved in the development of renal disease, integration of the gene-centric and protein-centric general databases with those of human kidney tissue and urine proteomes may open a new window for research in nephrology. Proteins present in the kidney and urine provide basic tools for investigation of kidney function and disease. By comparing such databases between healthy and diseased populations, proteins involved in the development of renal disease or new biomarker candidate proteins can be identified [49].

Many quantitative proteomic techniques have been used in the apoptosis processing analyses, but the large amount and complex data sets are difficult to evaluate. To consolidate these data, Magnus develop an Apopto Proteomics database for storing, browsing and analyzing the outcome of large-scale proteome analyses to apoptosis, which is available at http:// apoptoproteomics.uio.no. The proteomics data of 52 publications are integrated and unified with protein annotations from UniProt-KB, the caspase substrate database homepage (CASBAH), and gene ontology [1].

Chlamydia is a virulent pathogen that resides in humans, birds and a wide range of animals [50]. It has been difficult to study because of its obligate intra cellular growth habit and lack of a genetic transformation system. Following the full genome sequencing of seven strains of Chlamydia and a rapid expansion of genomic, transcriptomic and proteomic analysis of these pathogens have been completed. The Chlamydia Interactive Database (CIDB) can be cross-queried by researchers for patterns in the data (http://www3.it.deakin.edu.au:8080/CIDB/) [51]. Combining the data of many research groups into a single database and cross-querying from different perspectives should enhance our understanding of the complex cell biology of these pathogens.

Comparison between induction of apoptosis by the intrinsic and the extrinsic signaling pathway revealed slight differences [1]. Furthermore, proteomics has significantly contributed to the field of apoptosis. Regardless of all the pressing challenges, there is no doubt that proteomic as a holistic measure of organism response to exogenous stressors will continue to make a great impact in biological process.

Challenges in proteomics

Although 2DE and 2D-DIGE technologies are the best available approaches for genuine top-down studies, including the analyses of post translational modifications, de novo sequencing, protein identification independent of genome sequences, establishing direct information on intact proteins, and studies of protein isoforms [52-54], there are also some challenges associated with it.

Under many physiological and pathological conditions, some important regulatory proteins secreted into the serum by the body undergo quantitative or qualitative changes. Unlike liver or kidney, the serum is easy to achieve in clinical, leading the blood proteome to achieve a comprehensive assessment of multiple-organ as possible [55], this is a reason that serum has been used in numerous diagnostic tests. However, the reared difficulties in making use of serum proteomics techniques to screen tumor serum protein markers.

On the one hand, various impurities should be removed to eliminate interference with the results; low abundance proteins are the most meaningful proteins and the presence of high abundance proteins affects the detection of low abundance proteins. The same difficulties exist either in cerebrospinal fluid (CSF) proteomics and milk proteomics [57-58]. On the other hand, proteomic analysis relies on sample stability and pretreatment, nevertheless different pretreatment methods or sample collection including sample storage time, storage temperature, frozen period, application of protease inhibitor and others may cause different effects, affecting the objectiveness and veracity of evaluating results [56]. Besides, as shown in table1, each of proteins separation and identification methods has their own advantages and disadvantages in the research of toxicology. 2D and MALDI-TOF-MS are suitable for fundamental research, while LC or SELDI-TOF-MS is often used in high throughput detection. It is clear that the resolution of the instrument is limited. Plenty of proteins that exist exceeding the detection limit of electrophoresis-assisted instrument. The need for developing more sophisticated off-gel proteomics and bioinformatics is increasingly warranted [59]. Meanwhile, it is also necessary to avoid the cross-reaction between proteins or antibodies [60].

In recent years, researchers believe living organisms is regulated by proteins and non-coding RNAs from multiple controls, this gap in proteomics research could be overcome in the short-term with the use of multiple omics profiling technologies to acquire corroborative evidence [15,61]. It is not enough to reveal evidence only in one subject, but the networks combining multi-omics methods are premature for now at the least. It depends on the discovery of more comprehensive rules.

Regardless of all the pressing challenges, there is no doubt that proteomics as a holistic measure of cell apoptosis will continue to make great strides as an indicator for toxicological research, but its further development should provide more accurate and profound information, connecting seamlessly with other regulating factors.

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References

1. Magnus A, Bernd T. ApoptoProteomics, an Integrated Database for Analysis of Proteomics Data Obtained from Apoptotic Cells.Mol Cell Proteomics. 2012; 11: 1-15.
2. Sanz AB, Santamarta B, Ruiz-Ortega M, Egido J, Ortiz A. Mechanisms of renal apoptosis in health and disease. J Am Soc Nephrol. 2008; 19: 1634-1642.
3. Mark R, Gerald MC. Apoptosis and Necrosis in Toxicology: A Continuum or Distinct Modes of Cell Death. Pharmacol Ther. 1997; 75: 153-177.
4. Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, et al. etaular Cell Biology. 5th edn. New York: WH Freeman and Company. 2004.
5. Peter J. Protein identification in the post-genome era: the rapid rise of proteomics. D Biophysics. 1997; 30: 279-331.
6. Jorg R, Albert S. Proteomics, Methods in Molecular Biology. Berlin: Humana Press. 2009.
7. Anderson NL, Anderson NG. Proteome and proteomics: new technologies, new concepts, and new words.Electrophoresis. 1998; 19: 1853-1861.
8. Thiede B, Rudel T. Proteome analysis of apoptotic cells. Mass Spectrom Rev. 2004; 23: 333-349.
9. Chuthaphisith S, Layfield R, Kerr ID, Erimin O. Principles of proteomics and its applications in cancer. Surg-J R Coll Surg E. 2007; 5: 14-22.
10. Douglas RG. Means to an End: Apoptosis and other Cell Death Mechanisms. New York: Cold Spring Harbor. 2011.
11. Dennis AB, Yang N, Sidhartha DR. Apoptosis.Encyclopedia of Toxicology. 3th edn. Netherlands: Elsevier. 2014.
12. Dennis JO, Alan AD, Geoffrey N Maksym. Proteomic analysis of rat proximal tubule cells following stretch-induced apoptosis in an in vitro model of kidney obstruction. J Proteomics. 2014; 100: 125-135.
13. Shen XL, Zhang Y, Xu W, Liang R, Zheng J, et al. An iTRAQ-based mitoproteomics approach for profiling the nephrotoxicity mechanisms of ochratoxin A in HEK 293 cells. J Proteomics. 2013; 78: 398-415.
14. Zhang B, Shen XL, Liang R, Li Y, Huang K, et al. Protective role of themitochondrial Lon protease 1 in ochratoxin A-induced cytotoxicity in HEK293 cells. J Proteomics. 2014; 101: 154-168.
15. Qi X, Yang X, Chen S, He X, Harsh D, et al. Ochratoxin A induced early hepatotoxicity: new mechanistic insights from microRNA, mRNA and proteomic profiling studies. Sci Rep-UK. 2014; 4: 1-14.
16. Suja F, Pramanik BK, Zain SM. Contamination, bioaccumulation and toxic effects of perects of pe chemicals (PFCs) in the water environment: a review paper. Water Sci Technol. 2009; 60: 1533-1544.
17. Huang Q, Zhang J, Francis LM, Peng S, Tian M, et al. Pert al.MuXMu X acid induces apoptosis through the p53-dependent mitochondrial pathway in human hepatic cells: A proteomic study. ToxicolLett. 2013; 223: 211-220.
18. Russmann S, Kullak-Ublick GA, Grattagliano I. Current concepts of mechanisms in drug-induced hepatotoxicity. Curr Med Chem. 2009; 16: 3041-3053.
19. Wang C, Zhou J, Wang S, Ye M, Fan G, et al. Shotgun approach based comparative proteomic analysis of*levo*-tetrahydropalmatine-induced apoptosis in hepatocytes.ToxicolLett. 2010; 194: 8-15.
20. Brian CS, Kimberly RH, Maria SS. Review ofrecent proteomic application in aquatic toxicology.Environ Toxicol Chem. 2011; 30(2): 274-282.
21. Graves PR, Haystead TAJ. Molecular biologist's guide toproteomics. MicrobiolMolBiol Rev. 2002; 66: 39-63.
22. Pedro AO, Maribel EB, Tanya M, Stephen N, Witold W, et al. Proteomic Analysis of Propiconazole Responses in Mouse Liver: Comparison of Genomic and Proteomic Profiles. J Proteomic Res. 2010; 9: 1268-1278.
23. Bruno MO, Jens RC, Daniel MS. 2DE: The Phoenix of Proteomics. J Proteomics.2014; 104: 140-150.
24. Michela DM, Karen P, Serena L, Chantel T, Etienne W, et al. Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) Impairs the Regulation of Apoptosis in Megakaryocytes by Activating NF-κB: a Proteomic Study. Mol Cell Proteomics. 2011; 11: M111.007625.
25. Zhao J, Sun Z, Zhang X, Zhang Y, Liu J, et al. Mycobacterial 3-hydroxyacyl-l-thioester dehydratase Y derived from Mycobacterium tuberculosis induces COX-2 expression in mousemacrophages through MAPK-NF-κB pathway. Immunol Lett. 2014; 61: 125-132.
26. Maloney A, Workman P. Hsp90 as a new therapeutic target for cancer therapy: the story unfolds. Exp Opin Biol Ther. 2002; 2: 3-24.
27. Jin L, Xiao C, Lu C, Xia M, Xing G, et al. Transcriptomic and proteomic approach to studying SNX-2112-induced K562cells apoptosis and anti-leukemia activity in K562-NOD/SCID mice. FEBS Lett. 2009; 583: 1859-1866.
28. Nina K, Petra H, Radovan K. The progress of proteomic approaches insearching for cancer biomarkers. New Biotechnol. 2013; 3: 319-326.
29. Friedlander RM. Apoptosis and caspases in neurodegenerativediseases. N Engl J Med. 2003; 348: 1365-1375.
30. Eric T, Serge U, Oana V, Martail S, Nathalie G, et al. Quantitative proteomic analysis reveals protein expressionchanges in the murine neuronal secretome during apoptosis. J Proteomics. 2012; 77: 394-405.
31. George SK, Maria PP, Punit S, Natasha M, Annie X, et al. In-depth proteomic delineation of the colorectalcancer exoproteome: Mechanistic insight andidentification of potential biomarkers. J Proteomics. 2014; 103: 121-136.
32. Perroud B, Lee J, Valkova N, Dhirapong A, Lin PY, et al. Pathway analysis of kidney cancer using proteomics and metabolic profiling. Mol Cancer. 2006; 5: 64.
33. Ruiz Esparza-Garrido R, Velázquez-Flores MÁ, Diegopérez-Ramírez J, López-Aguilar E, Siordia-Reyes G, et al. Proteomic approach of pediatric astrocytomas: MiRNAs and network insight. J Proteomics. 2013; 94: 162-175.
34. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893-2917.
35. Hiroshi I, Tatsuo K, Kosugi SI, Yasuyuki K, Toshifumi W, et al. Proteomic and meta-transcriptomic study onlymph node metastasis in gastric cancer. Eupa open Proteomics. 2014; 3: 183-194.
36. Chang ET, Adami HO. The enigmatic epidemiology ofnasopharyngeal carcinoma. Cancer EpidemBiomar. 2006; 15: 1765-1777.

37. Yang J, Zhou M, Zhao R, Peng S, Luo Z, et al. Identification of candidate biomarkers for the early detection of nasopharyngeal carcinoma by quantitative proteomic analysis. J Proteomics. 2014; 109: 162-175.

38. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007; 176: 532-555.

39. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013; 187: 347-365.

40. Beasley V, Joshi PV, Singanayagam A, Molyneaux PL, Johnston SL, et al. Lung microbiology and exacerbations in COPD. Int J Chronic Obstr. 2012; 7: 555-569.

41. Pastor MD, Nogal A, Molina-Pinelo S, Meléndez R, Salinas A, et al. Identification of proteomic signatures associatedwith lung cancer and COPD. J Proteomics. 2013; 89: 227-237.

42. Chen H, Wang D, Bai C, Wang X. Proteomics-Based Biomarkers in Chronic Obstructive PulmonaryDisease.J Proteome Res. 2010; 9: 2798-2808.

43. Ohlmeier S, Mazur W, Linja-Aho A, Louhelainen N, Rönty M, et al. Sputum Proteomics Identifies Elevated PIGR levels in Smokersand Mild-to-Moderate COPD. J Proteome Res. 2012; 11: 599-608.

44. Steffen O, Minna V, Tuula T, Katri V, Kaisa S, et al. Proteomics of Human Lung Tissue Identifies Surfactant Protein A asa Marker of Chronic Obstructive Pulmonary Disease. J Proteome Res. 2008; 7: 5125-5132.

45. Belarmino JM, Kogan BA. Management of neonatalhydronephrosis. Early Hum Dev. 2006; 82: 9-14.

46. Cox H, Webster A. Translating biomedical science into clinical practice:molecular diagnostics and the determination of malignancy. Health (London). 2013; 17: 391-406.

47. Ziegler A, Koch A, Krockenberger K, Grosshennig A. Personalized medicineusing DNA biomarkers: a review. Hum Genet. 2012; 131: 1627-1638.

48. Sahar H, Harald M, Qannari EM, Mohamed H, Grethe IB, et al. Analysis of omic data: Graphical interpretation-and validation tools in multi-block methods. Chemometr Intell Lab. 2010; 15: 140-153.

49. Tadashi Y. Proteomics Database in Chronic Kidney Disease. Adv Chronic Kidney D. 2010; 17: 487-492.

50. Schachter J, Stamm WE, Quinn TC, Andrews WW, et al. Ligase chain reaction to detect *Chlamydia trachomatis* infection of the cervix. J Clin Microbiol. 1994; 32: 2540-2543.

51. Chen Y, Timms P, Chen YP. CIDB: Chlamydia Interactive Database for cross-querying genomics, transcriptomics and proteomics data. Biomol Eng. 2007; 24: 603-608.

52. Rogowska-Wrzesinska A, Le Bihan MC, Thaysen-AndersenM, Roepstorff P. 2D gels still have a niche in proteomics. J Proteomics. 2013; 88: 4-13.

53. Martins-de-Souza D, Guest PC, Vanattou-Saifoudine N, Harris LW, et al. Proteomic technologies for biomarkerstudies in psychiatry: advances and needs. Int Rev Neurobiol. 2011; 101: 65-94.

54. Otte DM, Bilkei-Gorzó A, Filiou MD, Turck CW, Yilmaz O, et al. Behavioral changes in G72/G30 transgenicmice. Eur Neuropsychopharm. 2009; 19: 339-348.

55. Sun B, Utleg AG, Hu Z, Qin S, Keller A, et al. Glycocapture-assisted global quantitative proteomics (gagQP) reveals multiorgan responses in serum toxicoproteome. J Proteome Res. 2013; 12: 2034-2044.

56. Liu W, Yang Q, Liu B, Zhu Z. Serum proteomics for gastric cancer. Clin Chim Acta. 2014; 431: 179-184.

57. Jan O, Bo F, Kerstin N, Lars IA, Mohsen K, et al. Multiple sclerosis: Identification and clinical evaluation of novel CSF biomarkers. J Proteomics. 2010; 73: 1117-1132.

58. Paloa R, Cristian P, Alessio S, Romana T, Andrea U, et al. Farm animal milk proteomics. J Proteomics. 2012; 75: 4259-4274.

59. Giancarlo R, Oladele O, Laura G, Mariarita A. Environmental proteomics: A long march in the pedosphere. Soil Biol Biochem. 2014; 69: 34-37.

60. Tammen H, Hess R, Schulte I, Kellmann M, Appel A, et al. Prerequisites forpeptidomic analysis of blood samples: II. Analysis of human plasma after oralglucose challenge-a proof of concept. Comb Chem High T Scr. 2005; 8: 735-741.

61. Emmanuelle C, Eric B, Marchandeau JP, Arnd B, Susanne S, et al. Integrated transcriptomic and proteomic evaluation of gentamicin nephrotoxicityin rats. Toxicol Appl Pharm. 2012; 258: 124-133.

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