

Proteomics: Concepts and applications in human medicine

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Author contributions: Al-Amrani S drafted the first draft and approved the final version; Al-Jabri Z, Al-Zaabi A, Alshekaili J, and Al-Khabori M critically edited the manuscript and approved the final version.

Conflict-of-interest statement: All authors declare no conflict of interest.

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Manuscript source: Invited manuscript

Specialty type: Biochemistry and

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Abstract

Proteomics is the complete evaluation of the function and structure of proteins to understand an organism's nature. Mass spectrometry is an essential tool that is used for profiling proteins in the cell. However, biomarker discovery remains the major challenge of proteomics because of their complexity and dynamicity. Therefore, combining the proteomics approach with genomics and bioinformatics will provide an understanding of the information of biological systems and their disease alteration. However, most studies have investigated a small part of the proteins in the blood. This review highlights the types of proteomics, the available proteomic techniques, and their applications in different research fields.

Key Words: Proteomics; Biomarker; Mass spectrometry; Two-dimensional electrophoresis; Drug discovery

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Core Tip: Proteomics is the complete evaluation of the structure and function of proteins to understand an organism's nature. Mass spectrometry is an essential tool that is used to profile proteins in the cell. However, biomarker discovery remains the major challenge of proteomics because of the complexity and dynamicity. This review highlights the types of proteomics, the available proteomic techniques, and their applications in different research fields.

molecular biology

Country/Territory of origin: Oman**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: February 22, 2021**Peer-review started:** February 22, 2021**First decision:** April 20, 2021**Revised:** May 4, 2021**Accepted:** July 15, 2021**Article in press:** July 15, 2021**Published online:** September 27, 2021**P-Reviewer:** Suriyaphol G**S-Editor:** Gao CC**L-Editor:** Filipodia**P-Editor:** Yuan YY**Citation:** Al-Amrani S, Al-Jabri Z, Al-Zaabi A, Alshekaili J, Al-Khabori M. Proteomics: Concepts and applications in human medicine. *World J Biol Chem* 2021; 12(5): 57-69**URL:** <https://www.wjgnet.com/1949-8454/full/v12/i5/57.htm>**DOI:** <https://dx.doi.org/10.4331/wjbc.v12.i5.57>**INTRODUCTION**

Proteomics is a new type of 'omics' that has rapidly developed, especially in the therapeutics field. The word proteome was created by Marc Wilkins in 1995[1]. Proteomics is the study of the interactions, function, composition, and structures of proteins and their cellular activities[2]. Proteomics provides a better understanding of the structure and function of the organism than genomics. However, it is much more complicated than genomics because the protein expression is altered according to time and environmental conditions[3]. It is estimated that there are almost one million human proteins, many of which contain some modifications such as post-translational modifications (PTMs). However, it is also estimated that the human genome codes for about 26000-31000 proteins[4]. There are a variety of proteomics techniques including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis (2-DE)[5], as well as gel-free high-throughput screening technologies such as multidimensional protein identification technology[6], stable isotope labeling with amino acids in cell culture[7], isotope-coded affinity tag, and isobaric tagging for relative and absolute quantitation [8]. Shotgun proteomics[9], 2D difference gel electrophoresis (2D-DIGE)[10], and protein microarrays[11] can be used in tissues, organelles, and cells. Large-scale western blot assays[12], multiple reaction monitoring assays[13], and label-free quantification of high mass resolution liquid chromatography (LC)-tandem mass spectrometry (MS) are commonly used for high-throughput processing. In the last decade, proteomics has been classified into protein expression mapping and protein interaction mapping[14]. The former method uses 2-DE combined with MS for quantitative proteome expression in cells, body fluids, or tissues. Protein expression mapping can provide an understanding of the PTMs of expressed proteins under different environmental conditions or disease states[14]. Protein-protein interaction mapping uses the yeast two-hybrid system coupled with MS to determine the interaction partners for each cell's encoded proteins and the proteome-wide scale[15].

Proteomics is a multi-step technique in which every step should be very well controlled to avoid non-biological factors interfering with protein expression and interaction. Sample preparation is the most important step because it solubilizes all proteins in the sample and eliminates all interfering inhibitory compounds such as lipids. Adequate sample preparation is crucial to obtain reliable, accurate, and reproducible results[16]. PAGE is the most widely used method for protein separation and isolation[17]. High-performance LC (HPLC)[18], 1-DE, and 2-DE are the methods used to separate proteins[19]. Proteins are isolated using 1-DE based on their molecular mass. Protein solubility is rarely an issue since proteins are solubilized in sodium dodecyl sulfate (SDS).

Furthermore, 1-DE is easy to use, repeatable, and capable of resolving proteins with molecular masses ranging from 10 kDa to 300 kDa[17]. As 1-DE gel has minimal resolving power, it is most commonly used to characterize proteins after being purified. However, in more complex protein mixtures, such as a crude cell lysate, 2-DE may be used. In 2-DE, proteins are determined by their net charge and their molecular mass[17].

Proteomics can analyze the expression of a protein at different levels allowing the assessment of specific quantitative and qualitative cellular responses related to that protein[20]. Qualitative and quantitative proteomes are measured at post-transcriptional, transcriptomic, and genomic levels[21]. According to the conditions, qualitative proteomics utilizes microarrays, 2-DE, and 2D-LC to monitor protein mixture composition and protein expression changes[20]. In addition, it can provide information on the molecular mechanisms of diseases and compare two groups such as patients with healthy controls[20]. Quantitative proteomics can also provide deep insights into disease mechanisms, cellular functions[22], and biomarker discovery[23]. Several new strategies are used in quantitative proteomics, such as post-extraction or metabolic stable-isotope labeling alone or in combination with affinity labeling[24,25]. MS identifies compounds by sorting cations according to their mass-to-charge ratio[26].

The study of proteomics has many applications in different fields such as medicine, oncology, food microbiology, and agriculture. This review will shed light on proteomics, their techniques, some of its applications, and the challenges currently faced in this field.

TYPES OF PROTEOMICS

Proteomics has three main types: expression proteomics, functional proteomics, and structural proteomics[27].

Expression proteomics

Expression proteomics is a novel approach that studies the quantitative and qualitative expression of proteins. It aims to specify the difference in protein expression between two conditions such as patients and controls[28]. In addition, it can identify disease-specific proteins and new proteins in signal transduction[17]. Expression proteomics experiments are usually used to study the patterns of protein expression in different cells. For example, a tumor tissue sample is compared to a normal tissue sample to identify differences in the levels of proteins[26]. Variations in protein expression, which are present or missing in tumor tissue compared to normal tissue, are detected using 2-DE and MS techniques[29].

Structural proteomics

Nuclear magnetic resonance spectroscopy and X-ray crystallography are used in structural proteomics to determine the three-dimensional structure and structural complexities of functional proteins. It specifies all protein interactions such as membranes, cell organelles, and ribosomes in the mixture[30]. The study of the nuclear pore complex is an example of structural proteomics[31].

Functional proteomics

This type of proteomics studies the protein functions and molecular mechanisms in the cell and determines the protein partner's interactions. In particular, it investigates the interaction of an unknown protein with partners from a specific protein complex involved in a particular process. This may indicate the biological role of the protein [32]. In addition, the elucidation of protein-protein interactions *in vivo* can lead to comprehensive descriptions of cellular signaling pathways[33].

PROTEOMICS WORKFLOW

Two methods can be used in proteomics: top-down and bottom-up workflows. The bottom-up method is sometimes called peptide-based proteomics. Here, the protein is digested by trypsin and separated by a specific column, followed by analysis of the peptides by MS[15]. The bottom-up approach can be classified into two groups according to the fractionation step. The first approach uses 2-DE to isolate the proteins from the gel. Then the proteins are digested into peptides that MS can identify. The second approach is called "shotgun" proteomics. Here, the digestion of protein occurs without fractionation, and LC is used to separate the peptides identified by MS[34]. In top-down proteomics, whole proteins or polypeptides are immediately assessed by MS. The molecular mass of proteins is sometimes calculated by using electrospray ionization (ESI) followed by matrix-assisted laser desorption/ionization (MALDI) MS [35]. Top-down proteomics can identify proteins with a molecular mass of > 200 kDa [36]. Both approaches have various advantages and limitations. In the bottom-up approach, there is low percentage coverage of the protein sequence, because the recovered sample includes small and inconsistent fractions of total peptides. This results in missing a large proportion of alternative splice variants and PTMs. However, in top-down proteomics, all characteristics of proteins are protected, and almost all existing modifications and correlations can also be recovered. Moreover, in top-down proteomics, the results of the exclusion of protein digestion with time are preserved [37]. The major challenge in top-down proteomics is the poor solubility of proteins compared to small peptides. Some proteins in the membrane have high solubility but need to be washed with SDS; however, SDS cannot be used in ESI[38]. Proteomics workflows involve sample preparation and analytical flow. The latter include separation of proteins, protein identification, and validation.

Sample preparation

Proteomics experiments highly depend on the accuracy of sample preparation, in addition to a well-designed pre-analytical workflow. There is no standard technique for sample preparation in proteomics. Each method depends on the number of proteins in the sample, the sample's complexity, and the study's objectives. Extraction of proteins from the mixture is the most vital step in the preparation of samples. To maximize protein extraction and solubilization, the extraction should include organic solvents and detergents followed by a tissue disruption technique. The organic solvents and detergents can be removed by lyophilization[39]. In previous detergent-based methods, the extraction of 2,2,2-trifluoroethanol (TFE) macro-scale (> 100 µg) materials and nano-scale (30 µg)-based lysis have provided comparable protein detection rates[40].

Separation and isolation of protein

Gel-based and chromatography-based approaches are used for the separation and isolation of proteins from the mixture.

Gel-based approach

The best technique for protein isolation and detection is PAGE[41]. For separation, 1-DE and 2-DE can be used. Furthermore, 2D-DIGE and SDS-PAGE are examples of 2D variations used in gel electrophoresis[42].

1-DE

1-DE, can isolate proteins with a molecular weight of 10 kDa to 300 kDa. It uses SDS, a detergent that denatures secondary and non-disulfide-linked tertiary structures, and combines them with a negative charge proportional to their volume. This allows the calculation of molecular weights[43]. SDS-PAGE can be used to verify the purity of samples, test protein purification, and calculate molecular weights for unknown proteins[44].

2-DE

2-DE differentiates proteins better than 1-DE due to the variation in molecular weight and isoelectric point of protein molecules[43]. It also has a better resolution than 1-DE because the protein is separated into two different dimensions. In 1-DE, the protein is separated based on net charge, but in 2-DE, protein separation is based on the molecular mass and isoelectric point. Thus, this method can detect different forms of proteins such as PTMs and phosphorylation. Some proteins that arise from different proteolysis processes and splicing of alternative mRNA can be resolved by 2-DE[45]. There are many applications of 2-DE, including protein expression profiling and cell map proteomics. Protein expression profiling can be used for comparing normal and diseased tissues. Mapping proteins in 2-DE can be used in cellular organelles[46], protein complexes[19], and microorganisms[47]. 2-DE can help catalog proteins, and the database can be created on the World Wide Web[48]. However, 2-DE cannot detect proteins at a low molecular weight and the limits of separation by isoelectric point and size[49].

Chromatography-based approach

Chromatography of affinity, size exclusion chromatography (SEC), and ion-exchange chromatography (IEC) techniques can be used to purify protein-based chromatography. In addition, western blotting and the enzyme-linked immunosorbent assay are used to identify selective proteins[50].

IEC

IEC is used to purify proteins according to their charges. This technique allows separating proteins according to their charge nature, which is not possible by other approaches. The charge accepted by the molecule of interest can be readily used by altering the pH of the buffer. The IEC technique is low cost and can persist in variable buffer conditions[30].

SEC

SEC can be used to separate different compounds according to their size (hydrodynamic volume) measured by how efficiently they enter the stationary phase's pores. However, this technique is not as useful as other proteomics techniques[51]. Two basic versions of SEC are utilized: gel permeation chromatography (GPC) using organic

solvents, which is used for polymer analysis; and gel filtration, which is performed using aqueous solvents.

Affinity chromatography

Affinity chromatography is the process of protein separation according to its interaction with an immobilized ligand. In 2-DE and non-2-DE, affinity chromatography helps decrease the protein complexity[52]. There are three types of affinity chromatography: separation of protein before 2-DE, affinity chromatography of protein before MS, and affinity chromatography of peptides before MS.

LC

LC is a powerful technique that can separate proteins from a complex mixture and can analyze large and fragile biomolecules. When combined with MS, it can be used for determining the peptides in the mixture[53]. LC can help researchers discover novel biomarkers and understand the mechanisms of carcinogenesis according to the modification of proteins. For example, some researchers use LC-MS/MS to rapidly monitor congenital adrenal hyperplasia from dried filter-paper blood samples[54].

Protein identification and characterization

The identification of proteins is a critical step in proteomics. MS can be used after the separation of the proteins by chromatography or electrophoresis[55]. Other techniques can also identify proteins such as Edman sequencing and protein microarray[17].

Edman sequencing

Edman sequencing has been used to detect the sequence of amino acids in peptides or proteins. This technique includes the reaction of chemicals, which remove and determine amino acid residues present at the N-terminus of the polypeptide chain. Thus, it plays a significant role in assessing biopharmaceutical quality and therapeutic proteins[17].

MS

MS is the best analytical tool for rapidly facilitating the sequencing of proteins[56]. It can also be used to detect the molecular weight of proteins. In this technique, protein molecules are ionized, and their mass is calculated according to mass-to-charge ratios. The mass spectrometer has three main components: an analyzer, an ion source, and a detector. The methods used for ionization are ESI and MALDI[57]. In MALDI, a chemical matrix is mixed with the peptides, and spotted onto a metal multiwell micro-liter plate to make a crystal lattice. The matrix chemicals pass the energy to the samples after absorbing it. Then peptide ions are detected by a mass analyzer. MALDI creates mostly singly charged ions that help to determine the m/z value[58]. In ESI, the power is activated in the protein sample to create charged droplets that increase gaseous ion production, which then are analyzed with a mass analyzer[59]. The advantages of ESI are its high reproducibility and high elasticity to combine many categories of MS. Furthermore, ESI can be fixed to time-of-flight (TOF)-MS, quadruple, ion traps, and fourier transform ion cyclotron resonance. On the other hand, the disadvantages of ESI are that it cannot be applied for molecular imaging, it requires a large quantity of samples, and multiple peaks are produced due to the many charged ions that result in the complexity of MS/MS spectra[60].

Protein identification and validation

Sequent, Mascot, Comet, and Tandem are instruments currently available for database searching[61]. However, most search devices do not produce matching data as they operate on differentiation algorithms and recording functions, creation integration, and data comparison from many studies and experiments. As a result, the identification of peptides by data search needs additional time[62]. High-quality data makes the data search more effective and less time consuming. Moreover, using accurate mass to measure ion fragments can shorten database explorations and produce more accurate results[63].

BIOINFORMATICS IN PROTEOMICS

Bioinformatics analyses use novel proteomics algorithms to manage the large and varied data in the process of marker discovery[64]. Controlling this massive quantity

of data and finding the association between other omics technologies (*e.g.*, metabolomics and genomics) remain difficult. The analyses of proteomics data is challenging because of the parameters used in processing, quality valuation, and shortage of standards for data formats. The big challenge is how to analyze massive data and create real biological understanding[65]. Protein pathways are a collection of internal cell reactions that have a specific biological impact. For protein pathways, a variety of tools and databases are available[66]. The Kyoto Encyclopedia of Genes and Genomes, BioCarta, Pathway Knowledge Base Reactome and Ingenuity pathway databases have extensive information on metabolism, signaling, and interactions[67,68]. Unique databases for signal transduction pathways, such as GenMAPP or protein analysis through evolutionary relationships (PANTHER), have been created[69,70]. Furthermore, databases such as Netpath, which include cancer-related pathways, have been created to detect proteins unique to a specific cancer type[71]. Details about protein interactions in complexes can be found in databases including BioGRID, IntAct, MINT, and HRPD [72-74]. The STRING database links to various other databases for literature mining and is commonly used for protein interaction. Furthermore, using the STRING database, protein networks can be drawn based on the list of genes given and the available interactions[75,76].

APPLICATIONS OF PROTEOMICS IN MEDICINE

Proteomics is a revolutionary technique that has been used in medicine, including drug and biomarker discovery. Proteomics can identify and monitor biomarkers by analyzing the proteins in the body fluids such as urine, serum, exhaled breath and spinal fluid. Proteomics can also facilitate drug development by providing a comprehensive map of protein interactions associated with disease pathways[77].

Biomarker discovery

A biomarker is an assessable pointer of a normal or abnormal biological state in the body[78]. In clinical settings, cancer development and its response to therapy are measured by cancer biomarkers[79]. 2D-PAGE is used for the discovery of biomarkers. It can also compare the profiles of proteins in normal and diseased cells such as tumor tissues and body fluids[80]. Cancer biomarkers are divided into three classes, predictive, prognostic and diagnostic, based on their uses. Predictive biomarkers can predict the response to therapy. For instance, in breast cancer, the activation and the positivity of human epidermal growth factor receptor 2 can predict the response to trastuzumab[81]. In addition, in colorectal cancer, mutation of Kirsten rat sarcoma virus gene can predict resistance to treatment with epidermal growth factor receptor inhibitors (*e.g.*, cetuximab)[82].

On the other hand, prognostic biomarkers can provide physicians with a prediction of the clinical outcomes. For example, the 21-gene repetition mark predicts breast cancer relapse and complete survival in node-negative, tamoxifen-treated breast cancer[83]. The third group of biomarkers is the diagnostic biomarker, which indicates if a patient has a specific disease condition. For example, in colorectal cancer, a stool DNA test is used as a diagnostic biomarker[84]. These biomarkers can be found in tissues, serum, blood, and urine. The body-fluid sampling for proteomics is thus less invasive and low cost. The discovery of biomarkers has progressed in many diseases such as acquired immune deficiency syndrome, cardiovascular diseases, diabetes, cancer, and renal diseases[85,86]. However, the highly complex mixtures of proteins and the high range of protein dynamics are examples of challenges in fluid sampling for proteomics. Each type of sample has a different usage according to the disease conditions. For instance, in kidney disease, the urine sample is used to assess urine proteins, reflecting changes in kidney functions[87]. In other human diseases, blood is also used for biomarker discovery. There are some challenges for using the plasma in biomarker discovery, such as protein dynamicity, the variation of the patient[87], and the low abundance of biomarkers in plasma. These challenges in biomarker discovery have yet to be addressed[88]. Most biomarker discovery studies are focused on cancer-related diseases due to their clinical importance. For instance, many biomarkers are associated with tumors that can be used to follow up with the patients[89].

Drug discovery

Drug discovery is a complex process with many different stages including chemical, functional, and clinical proteomics-based approaches. The application of proteomics in drug discovery has been developed to include patients' treatment and care[90]. 2-DE

cannot be used in drug discovery because it fails to separate the membrane proteins that characterized about 50% of important drug targets[91]. Moreover, 2-DE cannot detect low-abundance proteins[90]. In drug discovery proteomics, understanding the function of proteins and their interactions in the mixture is very important. Also, the methods should be able to detect low-abundance proteins and their activity. Therefore, many technologies such as MS and protein-chip have been used to identify and separate phage proteins. In addition, other techniques such as activity-based assays and two-hybrid assays can be used for the same purpose[92]. Using 2D-PAGE-MALDI-TOF/TOF, *Lavandula angustifolia* was used as a drug to treat Alzheimer's disease in rats[93].

Oncology

The application of proteomics in cancer is called oncoproteomics. Oncoproteomics can be used to identify anticancer drugs and the personalization of cancer management [94]. Microarrays and laser capture microdissection (LCM) of the tumor tissue can classify proteins in cancer. Oncoproteomics applications are used in many tissues such as the colon, breast, rectum, prostate, and brain. In addition, proteomics can be used to diagnose cancer and discover novel therapies[95]. Many proteomics techniques can be used to detect biomarkers in cancer such as aptamer-based molecular probes, cancer immunomics, tissue microarrays, nano-proteomics (to isolate signatures of autoantibodies), and antibody microarrays[94].

Two approaches can be used in tumor proteomics, LCM and MS imaging (MSI)[96]. LCM can separate the target proteins from the areas within the tumor before analysis with MS. In addition, this approach can help to determine proteins that correlate with tumor progression in the early and late stages of the disease using the proteinChip SELDI system®[97]. However, fewer studies use tumor tissues than serum due to the technical difficulties and low throughput using tumor tissues.

The second approach is using MSI. This direct tissue technique allows placing a small amount of MALDI matrix mixed directly with a fresh piece of the tumor[98]. This approach can help to map small molecules and proteins in a 3D view. This approach was to map eight normal lung tissues with 42 lung tumors[99]. Additionally, MSI can predict diagnosis, categorize lung cancer histology, and organize 85% of the nodal connections[96].

Leukemia

Proteomics was used to discover many leukemia biomarkers that could determine types of leukemia. Examples of these biomarkers include catalase, annexin 1, alpha-enolase, annexin A10, tropomyosin, tropomyosin 3, peroxiredoxin 2, and RhoGDI2. These biomarkers help to predict the diagnosis and outcome of the disease[100]. In addition, the proteomics approach can help developing new treatment pathways for leukemias using their proteomics profiles[101]. However, a major limitation of this approach is that important proteins controlling key cellular elements are present in low abundance and may not be readily detected.

Acute myeloid leukemia and proteomics

Acute myeloid leukemia (AML) is an aggressive blood cancer. Patients reach complete remission after intensive chemotherapy given as induction and consolidation[102]. However, relapsed AML may acquire at least one specific mutation such as FLT3, RUNX1, or ASXL1. Mutations in signaling genes such as KIT, NRAS, PTPN11, and NPM1 are less frequent[103]. The use of proteomics in AML may guide the post-induction strategy of either chemotherapy or allogeneic stem cell transplantation. Moreover, proteomics can help discover new or modified therapy options for AML patients[104]. Since the 1980s, many studies have focused on finding biomarkers in AML. For example, Hanash *et al*[105] used 2-DE to identify the cell of origin in acute leukemia.

While the prognosis of AML patients has improved through the years, especially in younger patients, mortality remains the highest among all other cancers[106]. Proteomics can assist the development of personalized therapy in AML[104]. Kwak *et al* [107] used 2-DE and MS to identify eight differentially expressed proteins between 12 healthy people and 12 patients with AML. Proteasome 26S ATPase subunit, immunoglobulin heavy-chain variant, and haptoglobin-1 were upregulated, while five proteins (unknown protein, lipoprotein C-III, RBP4 gene product, SP-40 and α -2-HS-glycoprotein) were downregulated[107]. Another study identified seven other proteins. These proteins were annexin A10, alpha-enolase, tropomyosin 3, lipocortin 1 (annexin 1), peroxiredoxin 2, RhoGDI2, and catalase[108].

In a recent study, BCL11A expression was found to play a role in AML. The study included 292 AML patients. The study found a significant association between the laboratory variables and the levels of BCL11A. However, BCL11A was not associated with survival and complete remission[109].

Most studies in proteomics in AML were performed on peripheral blood cells and bone marrow samples at an early stage. However, one study compared AML at diagnosis, remission, and relapse. It concluded that the proteome expression at diagnosis and relapse is similar at a high protein concentration[79,110]. Another study that focused on AML (subtypes M1 and M2) compared patients with healthy individuals. Twenty-five proteins were characterized in the peripheral blood and bone marrow samples. The study found that 6-phosphogluconate dehydrogenase, Annexin III and L-plastin were only found in the M2 subtype. The annexin I and actin gamma 1 levels were found to correlate with drug resistance at relapse[111].

CHALLENGES OF PROTEOMICS

There are many challenges in proteomics. The major challenge is the broad change in protein expression with the environment and cell type[112]. In addition, there is no comparable proteomics method, unlike genomics, that uses polymerase chain reaction [113]. Moreover, protein activities are highly regulated post-translationally, which adds difficulty to proteomics[114]. Finally, the type of samples and sample preparation techniques are other challenges in proteomics that can significantly change the quality of MS data. For example, the protein and phosphoprotein levels in breast cancer tumor samples were affected by the sample manipulation technique and bio-specimen type [115].

CONCLUSION

Proteomics is a fast, sensitive technology that provides high proteome coverage. Expression proteomics, functional proteomics, and structural proteomics are the three major types of proteomics. There are two different workflows in proteomics: top-down and bottom-up proteomics. In addition, there are increasing uses of proteomics in the majority of biological sciences. Finally, proteomics can assist in finding new biomarkers in different diseases and discover new therapies.

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