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Recent progress in mass spectrometry proteomics for biomedical research

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Proteins are the key players in many cellular processes. Their composition, trafficking, and interactions underlie the dynamic processes of life. Furthermore, diseases are frequently accompanied by malfunction of proteins at multiple levels. Understanding how biological processes are regulated at the protein level is critically important to understanding the molecular basis for diseases and often shed light on disease prevention, diagnosis, and treatment. With rapid advances in mass spectrometry (MS) instruments and experimental methodologies, MS-based proteomics has become a reliable and essential tool for elucidating biological processes at the protein level. Over the past decade, we have witnessed great expansion of knowledge of human diseases with the application of MS-based proteomic technologies, which has led to many exciting discoveries. Herein we review the recent progress in MS-based proteomics in biomedical research, including that in establishing disease-related proteomes and interactomes. We also discuss how this progress will benefit biomedical research and clinical diagnosis and treatment of disease.

affinity purification, LC-MS/MS, mass spectrometry, shotgun proteomics

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INTRODUCTION

Over thousands years of human civilized history, physicians and researchers have made countless efforts to conquer diseases. Researchers have uncovered the molecular mechanisms of many diseases over the past century, mostly based on accumulated observations. However, determining how these mechanisms apply to the cause and development of diseases in individual patients has remained largely elusive. Over the past few decades, the DNA and RNA sequencing technologies, especially next-generation sequencing, fundamentally changed our view of diseases. These sequencing technologies are now widely used in clinical diagnosis, including that of genetic disorders, infectious diseases, and, most recently, complicated diseases such as cancer (Biesecker and Green, 2014; Ferrari et al., 2013; Wang and Wheeler, 2014). Investigators have formed large collaborative efforts to establish the human genomic landscape of complex diseases such as Alzheimer disease (Seshadri et al., 2010), cardiovascular diseases (O'Donnell and Nabel, 2011), and cancer (The Cancer Genome Atlas (TCGA) (McLendon et al., 2008; Bell et al., 2011; Koboldt et al., 2012) and the International Genome Consortium (ICGC) (Hudson et al., 2010)). These collaborations not only established correlations between the human genotypes and disease phenotypes and revealed many genetic mechanisms driving diseases but also suggested novel targeted therapies and precision medicine for individual patients.

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However, diseases are caused by a combination of genetic, epigenetic, and environmental factors. Therefore, the genetic features of patients do not always correlate with disease diagnosis and prognosis. This could be due to many issues, one of which is that predicting protein expression and functions based solely on genetic information is difficult, as proteins and their activities are frequently regulated at the post-transcriptional and posttranslational levels. Thus, monitoring proteins, their activities and interactions provides crucial insight into biological processes that is critical for biomedical research. To achieve that, proteomics approaches which systematically access these information were introduced, and now become one of the most important components of modern biomedical research.

APPLICATION OF MASS SPECTROMETRY TECHNIQUES TO BIOMEDICAL RESEARCH

The first attempt to systematically understand the proteome composition took place more than 40 years ago with the use of two-dimensional gel electrophoresis to separate and quantitate proteins from a relatively complicated mixture, the whole-cell lysates from *Escherichia coli* (O'Farrell, 1975). Afterward, investigators introduced other proteomic approaches, such as biochemical genomics (Martzen et al., 1999), proteome chips (Zhu et al., 2001), reverse-phase protein microarrays (Paweletz et al., 2001), activity-based protein profiling (Adam et al., 2002), and antibody-based techniques (Uhlen et al., 2010). Combining antibody-based proteomics with genomic data, researchers recently established a tissue-based map of the human proteome (Uhlen et al., 2015). However, a more robust and cost-effective method which precisely and simultaneously access the information on thousands of proteins over a wide dynamic range is needed.

Although mass spectrometry (MS) was invented more than a century ago, it has only been used in protein analyses over the past three decades. Using matrix-assisted laser desorption ionization (MALDI) and a time-of-flight (TOF) mass spectrometer, Tanaka and colleagues were the first to ionize and analyze large biomolecules such as proteins using MS (Tanaka et al., 1988). Since then, tremendous efforts have been devoted to expanding MS applications in proteomics in terms of its sensitivity, accuracy, dynamic range and throughput (Aebersold and Mann, 2003; Aebersold and Mann, 2016). MS-based proteomics now allows for measurement of the absolute or relative abundance of thousands of proteins all at once, exceeding other methods in throughput, sensitivity, or both. It also offers a nearly universal detection method with no specificity or sensitivity limits (Mann et al., 2013). A typical "shotgun" bottom-up workflow for MS-based proteomics is often composed of enzymatic digestion of proteins into peptides, liquid chromatography (LC) separation and tandem MS (MS/MS)-based measurement of peptides, followed by database searching. This strategy allows for direct identification of proteins in a complex mixture (Wolters et al., 2001) and is now a standard workflow in MS-based proteomics because of its robustness and accuracy (Aebersold and Mann, 2003).

Alternative methods are available for each step of this workflow, which are designed for different purposes. For example, for sample preparation, in addition to label-free quantitation of spectra, isotopical and chemical tag-labeled MS approaches are widely used to assess relative and absolute protein abundances in complex environments. These methods include stable isotope labeling by amino acids in cell culture (SILAC) (Ong et al., 2002), isobaric tags for relative and absolute quantification (iTRAQ) (Ross et al., 2004), and tandem mass tags (TMTs) (Dayon et al., 2008; Thompson et al., 2003). SILAC provides high-quality quantitative proteomic data. However, it requires culturing cells in isotope-containing culture media. The recent development of "super-SILAC" allows for quantitative proteomic analysis of human tissue samples by mixing SILAC-labeled cell lines with tissue samples (Deeb et al., 2012; Geiger et al., 2010; Geiger et al., 2011). Meanwhile, chemical labeling approaches such as iTRAQ and TMT add isobaric tags directly to enzyme-digested peptides and thus do not require cells growing in isotope-containing culture media. For example, using the TMT technology, as many as 54 samples can be tagged with different combinations of isobaric tags and analyzed in a single MS run, thereby accessing the relative protein abundance and/or modifications in each sample (Choe et al., 2007; Everley et al., 2013; Murphy et al., 2014). Therefore, they can be used to directly compare protein abundances and/or modifications in multiple tissue samples without pretreatment (Altelaar et al., 2013a).

When performing MS, three types of data acquisition are frequently used: data-dependent acquisition (DDA), data-independent acquisition (DIA), and targeted MS approaches. The traditional method is DDA, in which the mass-to-charge ratio (m/z) and selected numbers of fragmentation spectra of peptides are measured, searched in a library containing information on all known peptides, and the matched peptides are eventually assigned to proteins (Link et al., 1999). In recent years, the DIA model has been quickly developed and used in an increasing number of MS-based proteomic studies. In DIA, all the precursor ions in the given range are acquired for the fragmentation to achieve a higher coverage of MS/MS spectra than DDA (Chapman et al., 2014). To closely monitor the biologically important proteins and peptides in a complex mixture, investigators introduced targeted MS approaches, including selected reaction monitoring, multiple reaction monitoring (Kuhn et al., 2004), and parallel reaction monitoring (Peterson et al., 2012). In these approaches, selected peptides of interest identified from discovery screen-

ing are closely monitored over their chromatographic elution time to generate comprehensive spectra and improve their coverage.

Posttranslational modifications (PTMs) are also extremely important for determining protein functions. These modifications extensively regulate protein activity and stability and therefore serve as critical intermediates for signal transductions in living organisms. Assessing PTMs using traditional biochemical approaches is cumbersome and has extremely low throughput. MS-based proteomics has a great advantage over the traditional methods in monitoring PTMs, with higher throughput and wider dynamic range. Researchers have performed proteome-scale studies to assess global changes in PTMs, such as phosphorylation (Harsha and Pandey, 2010; Harsha et al., 2013; Macek et al., 2009; Nita-Lazar et al., 2008), ubiquitination and ubiquitin-like modifications (Kirkpatrick et al., 2005; Shi et al., 2011), acetylation (Mischerikow and Heck, 2011), methylation (Afjehi-Sadat and Garcia, 2013), glycosylation (Pan et al., 2011), and many others. PTM information can be acquired simultaneously with the whole-proteome profile. However, affinity enrichment using reagents or antibodies against proteins or peptides with certain modifications may greatly increase the sensitivity of the detection and thus generally has been used in studies with certain PTMs of interest. For instance, to access the phosphorylation proteomes, affinity enrichment can be performed at the protein level using anti-phosphotyrosine or anti-phosphoserine/threonine antibodies, or at peptide level using TiO_2 or immobilized metal affinity chromatography, or a sequential combination of both. Using affinity enrichment, DNA damage-induced phosphorylation (Beli et al., 2012; Bennetzen et al., 2010; Bensimon et al., 2010; Matsuoka et al., 2007; Stokes et al., 2007), ubiquitination (Elia et al., 2015; Messick and Greenberg, 2009) and acetylation (Elia et al., 2015) landscapes were established.

Taken together, these methods generate reliable measurement of proteomes and thus make establishment of comprehensive human proteomes feasible (Figure 1).

ESTABLISHING THE HUMAN PROTEOME LANDSCAPE USING MS-BASED PROTEOMICS

Using bottom-up proteomic approaches, investigation of human proteomes was initiated at the beginning of the century. These efforts started with analyses of proteomes of organelles and large cellular structures in human cells due to their relatively simple protein compositions in comparison with that of the whole-cell proteome (Brunet et al., 2003; Yates et al., 2005). For instance, the proteomes of heart mitochondria (Gaucher et al., 2004; Taylor et al., 2003), B-cell and melanoma-derived exosomes (Mears et al., 2004; Wubbolts et al., 2003), lysosomes of monocytic and breast cancer cells (Journet et al., 2002), and spliceosomes and nucleoli of HeLa cells (Andersen et al., 2002; Rappsilber et al., 2002) were established by 2004. Researchers in most of these studies used one- or two-dimensional gel electrophoresis, whereas some started using LC to further separate already purified organelle samples (Gaucher et al., 2004). Protein bands or spots were excised from gels, digested in gels with trypsin, and analyzed using MS. Tens to hundreds of proteins were identified in each study depending on how many bands or spots were collected. However, the throughput of this type of approaches is far from sufficient to build a comprehensive human proteome.

With the development of high-performance LC (HPLC) and hybrid Fourier transform MS instruments such as linear quadrupole ion trap-Orbitrap mass spectrometers (Makarov et al., 2006a; Makarov et al., 2006b), researchers started to establish the comprehensive proteomes of human cell lines. These studies were often combined with extensive prefractionation at protein of peptide level using different strategies to reduce sample complexity (Stasyk and Huber, 2004). In 2007, Hubner and colleagues identified 3,979 proteins from HeLa cell lysates using 12 fractions (Hubner et al., 2008). This number was further increased to 7,093 and 10,225 in their follow-up studies (Nagaraj et al., 2011; Wiśniewski et al., 2009). Also, Lundberg and colleagues identified more than 5,000 proteins in U2OS bone osteosarcoma cells, A-431 epidermoid squamous cell carcinoma cells, and U-251MG brain glioblastoma cells (Lundberg et al., 2010). Beck et al. identified and quantified more than 10,000 proteins in the U2OS cell line (Beck et al., 2011). Later, Geiger et al. performed a comparative proteomic analysis of 11 human cell lines and identified on average more than 10,000 proteins in each line (Geiger et al., 2012). Gholami et al. completed a global proteome analysis of the NCI-60 cell line panel (Gholami et al., 2013). Furthermore, Munoz et al. established the proteomes of human induced pluripotent stem cells and embryonic stem cells (Munoz et al., 2011). Investigators also have made efforts to reduce the high number of fractions while achieving the same depth of proteome coverage, using either ultralong gradients or additional reverse-phase separation steps (Ding et al., 2013; Köcher et al., 2011; Köcher et al., 2012; Thakur et al., 2011). In combining high-resolution isoelectric focusing with searching in a proteogenomic-based protein database generated by a six-reading-frame translation of the human genome, Branca et al. identified more than 13,000 proteins in the human A-341 cell line (Branca et al., 2014), a number approaching the theoretical total number of proteins expressed in this cell line based on mRNA sequencing data. Taken together, the results of these proteomics studies of cell lines set the stage for establishing a high-quality cell-type-resolved human proteome.

Additionally, researchers have performed proteome analyses of human body fluid and tissue samples since the very early days of biomedical research. Samples of human plasma, which is easily accessible, have been studied using many

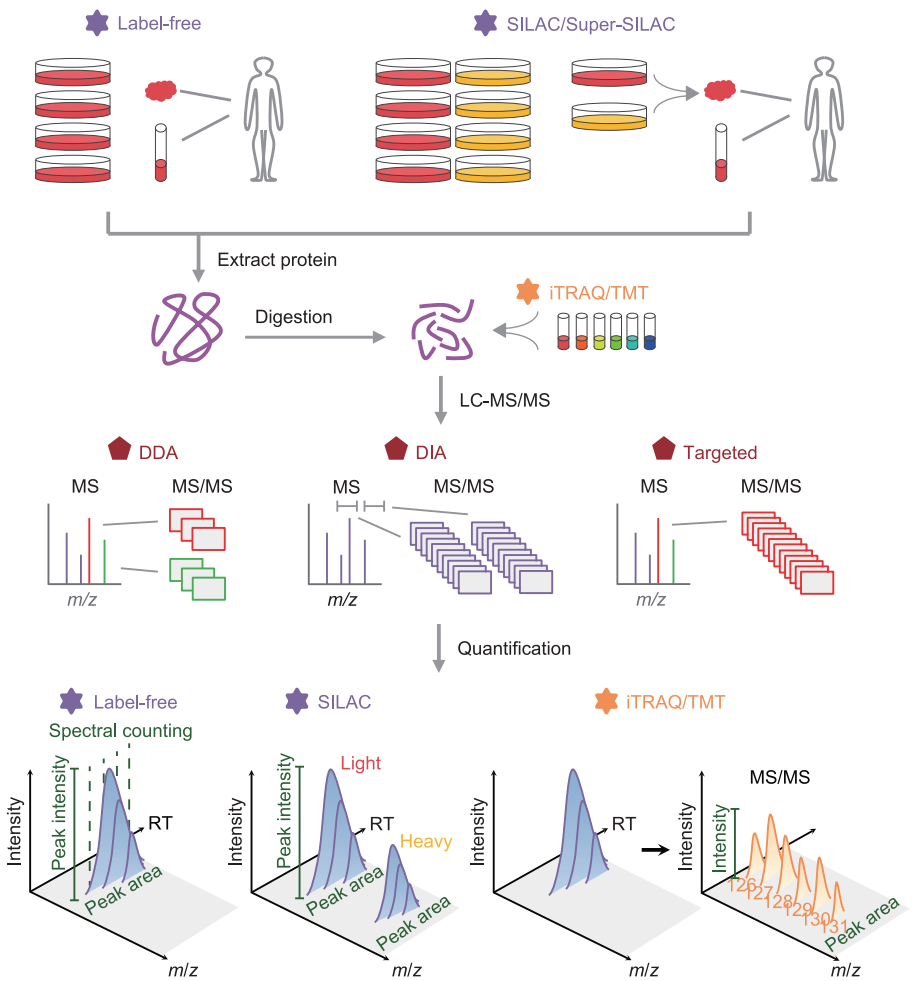

Figure 1 An integrated view of MS-based proteomic workflows. Step 0, cell lines are labeled with stable isotopes for SILAC experiments. Tissue or body fluid samples are labeled via mixing with stable isotope-labeled cells for super-SILAC experiments. This step is not necessary for label-free or isobaric labeling experiments. Step 1, proteins are extracted from cell, body fluid, or tissue samples. Step 2, they are then enzymatically digested into peptides and separated using LC and electrosprayed into a mass spectrometer. Samples may be subjected to fractionation before or after enzymatic digestion to separate certain fractions/organelles or reduce sample complexity. For isobaric labeling experiments, the peptides can be isobarically labeled using iTRAQ or TMT methods. Step 3, the MS mode, consisting of DDA, DIA, or targeted MS, is chosen. Step 4, data are analyzed and quantified. The *m/z* and MS/MS spectra are searched against protein sequence databases, and MS/MS spectra are assigned to peptides that can be subsequently mapped to proteins. Peptides and proteins can be quantified using label-free or relative/absolute quantification methods. Spectral counting, peak intensity, and peak area can be used for quantification. In DIA-based MS, the intensities of fragments that belong to the same precursor ion are extracted to measure the peptide abundance.

different methods for more than a century (Anderson and Anderson, 2002). Soon after MS was introduced into biomedical research, several studies using this technology identified a few hundred proteins in human plasma (Anderson and Anderson, 2002). Since then, investigators have made countless efforts to increase the coverage and reliability of the human plasma proteome (Farrah et al., 2011; Omenn et al., 2005; Schenk et al., 2008; States et al., 2006). In 2011, the Human Proteome Organization announced the completion of phases I and II of the Human Plasma Proteome Project, which identified 1,929 proteins with a 1% false-discovery rate (Farrah et al., 2011), and established a plasma proteome database (Nanjappa et al., 2014). Similarly to plasma, the human urine proteome has been extensively studied (Adachi et al., 2006; Kentsis et al., 2009; Li et al., 2010; Marimuthu et al., 2011; Nagaraj and Mann, 2011; Zerefos et al., 2012). The Human Urine Proteome Project was combined with a kidney proteome project (Cui et al., 2013; Magdeldin et al., 2016; Miyamoto et al., 2007) to form the Human Kidney and Urine Proteome Project. Both the Human Plasma Proteome Project and Human Kidney and Urine Proteome Project announced their future plans to explore the proteomes in disease states. Considering that plasma and urine samples are commonly used in routine clinical diagnosis of many diseases, these projects hold promise for revolutionizing disease diagnosis and therapy.

Proteomes of several other human organs have also been established. First announced in 2002 (He, 2005), the Human Liver Proteome Project generated a series of liver proteome data using LC-MS-based approaches (Chen et al., 2007;

Chinese-Human-Liver-Proteome-Profiling-Consortium, 2010; Ying et al., 2006). The high quality of these liver proteome data provided a solid foundation for the follow-up investigation of liver disease proteomes. Proteomes of different human brain regions also have been explored (Martins-de-Souza et al., 2014; Martins-de-Souza et al., 2008; Martins-de-Souza et al., 2009; Park et al., 2006). Recently established cell type and anatomically resolved mouse brain proteomes also generated valuable information for researches in brain development and function, and similar studies in humans can be conducted in the near future (Jung et al., 2017; Sharma et al., 2015). Finally, investigators completed two MS-based drafts of the human proteome in 2014 (Kim et al., 2014; Wilhelm et al., 2014). First, Kim et al. performed proteomic profiling of 30 histologically normal human samples, specifically, 17 adult tissue, seven fetal tissue, and six purified primary hematopoietic cell samples, and identified proteins encoded by 17,294 genes, which account for approximately 84% of all annotated protein-coding genes in humans (Kim et al., 2014). Second, Wilhelm et al. assembled data from 16,857 LC-MS/MS experiments involving human tissue samples, cell lines, and body fluid samples as well as data from PTM studies and affinity purifications (APs) and generated a draft of the human proteome covering 60 tissues types, 13 body fluids types, and 147 cell lines (Wilhelm et al., 2014).

These achievements should not be considered as the end of the exploration of human proteomes but rather the start of it. In 2010, the Human Proteome Project was announced (The-Human-Proteome-Organization, 2010); it was later expanded into the Biology/Disease-driven Human Proteome Project (Aebersold et al., 2013). This collaborative project started with 16 components, including organ proteomes such as the plasma, liver, brain, and kidney-urine proteomes, and disease proteomes, such as the cancer, diabetes, and infectious diseases proteomes (Aebersold et al., 2013). Completion of this project over the next few years will generate invaluable resources for biomedical research. More importantly, the ongoing and proposed disease proteome projects will greatly expand our understanding of human diseases and lead to novel approaches to clinical diagnosis of and therapy for them.

ESTABLISHING HUMAN DISEASE PROTEOMES FOR CLINICAL DIAGNOSIS AND THERAPY

The early attempts at using MS proteomics in clinical diagnostics date back to 2002. After comparing the surface-enhanced laser desorption and ionization time-of-flight (SELDI) spectra derived from analysis of serum samples obtained from 50 healthy women and 50 patients with ovarian cancer, Petricoin et al. reported a spectral pattern for ovarian cancer diagnosis using serum samples (Petricoin et al., 2002). This idea was broadly adopted for many other cancers over the next few years (Xiao et al., 2005). However, from an MS point of view, such attempts at using low-resolving-power MS in complex mixtures such as serum samples may only yield a subset of the most abundant low-mass peptides and protein fragments. Therefore, the patterns they established could belong to the same nonspecific proteins, which may not be relevant to the disease (Mann and Kelleher, 2008). Thus, researchers quickly realized that molecular signatures, especially quantitative peptide and protein identifications, are more reliable sources for diagnosis than are spectral patterns, especially because these molecular signatures are more comprehensive and can be independently validated using other methodologies, such as immunohistochemistry and Western blotting.

From there, researchers took different paths to establish comprehensive proteome signatures of human samples. Using MALDI-based imaging MS (Caprioli et al., 1997; Stoeckli et al., 2001), proteins can be ablated and directly analyzed in tissue sections (Cornett et al., 2007; Schwamborn and Caprioli, 2010). Hundreds of proteins can be semiquantitatively identified, even in formalin-fixed, paraffin-embedded samples (Lemaire et al., 2007; Ronci et al., 2008). Researchers have used MALDI-based MS imaging to elucidate molecular signatures in different tumor types, including brain, oral, lung, breast, gastric, pancreatic, renal, ovarian, and prostate cancers, and have identified several disease-related proteome signatures (Aichler and Walch, 2015; Schwamborn and Caprioli, 2010).

Meanwhile, much effort was devoted to establishing complete disease proteomes using shotgun proteomic approaches. By comparing proteomes of healthy individuals with those of patients with certain diseases, disease-related proteins were identified as novel biomarkers or drug targets. Several disease proteomes have been explored over the past decade. For example, brain (Andreev et al., 2012; Donovan et al., 2012; Musunuri et al., 2014), cerebrospinal fluid (Abdi et al., 2006; Choe et al., 2007), and plasma (Güntert et al., 2010) samples obtained from Alzheimer disease patients have been analyzed using label-free or iTRAQ MS approaches, and several potential biomarkers for the disease were identified. Also, extensive proteomic studies were performed using tissue and body fluid samples obtained from patients with cardiovascular diseases. The investigators identified many potential disease biomarkers, some of which overlapped traditional protein markers used in clinical diagnostics, indicating the potential of this type of research (de la Cuesta et al., 2015). A recent proteomic study of plasma proteomes of a cohort of 43 obese individuals who had experienced sustained weight loss revealed several potential biomarkers for monitoring interventions for metabolic diseases (Geyer et al., 2016).

The most extensively studied human disease proteomes are

cancer proteomes. Hundreds of proteomic studies using tissue and body fluid samples obtained from patients with almost all cancer types have been performed with the goal of identifying novel tumor biomarkers (Sallam, 2015; Tan et al., 2012). Quantitative MS was also used in these studies. Super-SILAC-based studies of breast tumors, brain tumors, and lymphomas have been performed, as well (Deeb et al., 2012; Geiger et al., 2010; Geiger et al., 2011). Furthermore, using iTRAQ-based LC-MS/MS, Hsu et al. identified and validated six potential biomarker proteins in a pool of 1,763 proteins (Hsu et al., 2016). These studies identified many potential cancer biomarkers and greatly expanded our knowledge of cancer proteomes. Unfortunately, many of these studies were performed in different laboratories using widely varying standards. Proper controls were frequently overlooked, and many abundant or nonspecific proteins were selected as biomarkers based on very limited numbers of patient samples.

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) was launched in 2011 (Whiteaker et al., 2014) with the ultimate goal of establishing high-quality quantitative proteomes of all cancer types using MS. They set standard shotgun proteomic workflows for all the participating laboratories in this consortium (Paulovich et al., 2010; Tabb et al., 2010). Within this framework, researchers conducted hundreds of studies to dissect disease proteomes. In particular, Kikuchi et al. performed label-free shotgun proteomic analysis of non-small cell lung cancer (Kikuchi et al., 2012). They identified 3,621 proteins in their analysis of pooled human squamous cell carcinoma, adenocarcinoma, and control samples. From there, they identified PAK2 as a significantly upregulated protein in non-small cell lung cancer samples. PAK2 may serve as a biomarker and drug target, as treatment with the PAK2 inhibitor IPA-3 has inhibited the migration and invasion of non-small cell lung cancer cell lines (Kikuchi et al., 2012).

However, an intrinsic problem with bottom-up workflows is the *m*/*z* and MS/MS spectra are used to search in knowledge-based database(s) to match with known peptides. This is usually effective when analyzing normal tissue samples. Unfortunately, diseases such as cancer are often associated with many genomic alterations and variations, which may hold the key to understanding the disease mechanisms. The proteins translated from these genomic variants cannot be matched with the information in a generic protein database. Thus, precious information of these mutated proteins is mostly lost during data analysis. Recent studies by the CPTAC introduced a proteogenomic concept to solve this problem. Specifically, deep sequencing data on samples are acquired and translated into amino acid sequences in six reading frames to create a customized protein database. Fragmentation mass spectra are searched against the protein database, and the identified peptides are statistically validated and evaluated to annotate novel proteins, detect disease variants, or systematically analyze protein variations (Alfaro et al., 2014; Sheynkman et al., 2016). This approach enables the discovery and quantitation of disease-specific proteomes for diagnosis and treatment.

Using this proteogenomic strategy, Zhang et al. analyzed 95 TCGA human colorectal cancer (CRC) samples using label-free shotgun LC-MS/MS and compared the results with sequencing results and the patients' clinical and pathological characteristics (Zhang et al., 2014). They identified a total of 7,526 proteins with a 2.64% false-discovery rate. Among them, they identified 108 somatic or Catalogue of Somatic Mutations in Cancer (COSMIC)-supported protein variants and mapped them to 105 genes, including several well-known cancer-related genes, such as *KRAS*, *CTNNB1*, *SF3B1*, *ALDH2*, and *FH*. These genes also included 14 targets of U.S. Food and Drug Administration-approved drugs or drugs in clinical trials, such as *ALDH2*, *HSD17B4*, *PARP1*, *P4HB*, *TST*, *GAK*, *SLC25A24*, and *SUPT16H*. Moreover, in this study, the investigators decoded the proteome signature of CRC and classified human CRC into five major proteomic subtypes (Zhang et al., 2014). Using a similar workflow, Zhang et al. analyzed 174 TCGA human ovarian cancer samples and identified a total of 9,600 proteins and 24,429 phosphorylation sites (Zhang et al., 2016). They also classified the tumors into subtypes based on their proteome signatures. They identified functionally relevant proteins, such as proteins associated with chromosomal structural abnormalities (Zhang et al., 2016). Using iTRAQ-based LC-MS/MS, Mertins et al. analyzed 105 TCGA human breast cancer samples (25 basal-like, 29 luminal A, 33 luminal B, and 18 ERBB2-enriched tumors) along with three normal breast tissue samples and identified a total of 15,369 proteins and 62,679 phosphorylation sites (Mertins et al., 2016). They observed proteome-wide copy-number alterations and classified the breast cancers into three proteomic subtypes based on their proteome signatures, which consisted basal-, luminal-, and stromal-enriched subtypes. Interestingly, mRNA-defined HER2-enriched tumors were distributed across these three proteomic subgroups (Mertins et al., 2016). Cherniack et al. performed genomic, epigenomic, transcriptomic, and proteomic characterization of uterine carcinosarcomas and established a multi-omics landscape of these tumors (Cherniack et al., 2017). Patient-derived xenograft models of breast cancer were also established using different MS-based approaches and several potential drug targets were identified (Huang et al., 2017; Ntai et al., 2016).

Researchers have also performed disease-oriented PTM proteomics studies, including phosphorylation (Harsha and Pandey, 2010), ubiquitination (Kessler, 2013), SUMOylation (Yang and Paschen, 2015) and glycosylation (Thaysen-Andersen et al., 2016). Taken together, these studies are excellent examples for future comprehensive proteomic studies of human cancers and other complex human

diseases.

ESTABLISHING PROTEIN-PROTEIN INTERACTION NETWORKS FOR HUMAN DISEASES

Besides the above mentioned applications, the other major application of MS in biomedical research is in exploring PPI networks. Dynamic signal transduction networks are the basis for controlled biological activities. These signaling cascades are extensively regulated by PPIs, which link upstream stimuli with downstream effectors. Studies of PPIs not only provide immense insight into individual protein functions but also delineate the highly dynamic biological processes, which are often altered in diseases. Moreover, the proteins encoded by the genes mutated in individuals with inherited genetic disorders are likely to interact with proteins known to cause similar disorders, suggesting the existence of disease-related PPI networks (Gandhi et al., 2006). Because of the importance of PPI, many biochemical tools have been invented to explore PPIs prior to MS, including *in vivo*/*in vitro* pull-down assays, co-immunoprecipitation assays using epitope tags or antibodies against endogenous proteins, cross-linking protein interaction assays, label transfer protein interaction analysis, and yeast two-hybrid analysis (Berggård et al., 2007; Vidal et al., 2011). In 2005, two human PPI networks were established using yeast two-hybrid approaches, which identified thousands of binary protein interactions (Rual et al., 2005; Stelzl et al., 2005).

Since then, AP-MS has gradually become the most used tool in exploring PPIs. By performing AP of a protein of interest (the "bait") using either affinity tags or antibodies, all the partner proteins (the "preys") that form complexes with the bait can be pulled down and identified using LC-MS/MS (Altelaar et al., 2013b). Unlike most of the traditional methods, AP-MS can identify protein complexes instead of binary interactions in organisms and cells with much higher throughput (Gingras et al., 2007). However, similar to other PPI exploring tools, AP-MS results suffer from a high rate of false-positive identifications. This is because abundant proteins, such as chaperones and ribosomal proteins, are frequently found in these results but are rarely functionally relevant (Mellacheruvu et al., 2013). Several post-MS data analysis algorithms and methods were developed to analyze label-free shotgun AP-MS data (Choi et al., 2011; Hauri et al., 2013; Li et al., 2016; Malovannaya et al., 2011; Mellacheruvu et al., 2013; Sardiu et al., 2008; Sowa et al., 2009; Varjosalo et al., 2013) with the goals of reducing the substantial noise in AP-MS results and generating a list of high-confidence candidate interacting proteins for the establishment of protein interactomes.

In 2007, Ewing et al. established an MS-based large-scale human interactome consisting of 338 bait proteins and 6,463 interactions among 2,235 proteins in HEK293 cells (Ewing et al., 2007). Using antibodies against endogenous proteins to perform immunoprecipitation followed by label-free shotgun MS, Malovannya et al. identified interacting partners for more than 1,000 human protein baits in HeLa cells. They detected about 100,000 interactions among 11,485 unique human gene products (Malovannaya et al., 2011). Havugimana et al. reported a census of human soluble protein complexes consisting of 13,993 interactions among 3,006 proteins in HeLa S3 and HEK293T cells (Havugimana et al., 2012). Recently, researchers established two drafts of human interactomes, which cover about 30% of human proteins as baits (Hein et al., 2015; Huttlin et al., 2015). Using label-free AP-MS against an human influenza hemagglutinin (HA) tag, Huttlin et al. identified interacting partners for 2,594 FLAG- and HA-tagged human protein baits in HEK293T cells and established a network of 23,744 interactions among 7,668 proteins (Huttlin et al., 2015). Using a similar workflow, Hein et al. identified interacting partners for 1,125 green fluorescent protein-tagged human protein baits in HeLa cells and established a network of 28,500 interactions among 5,400 proteins (Hein et al., 2015). We expect establishment of the complete human interactomes in HEK293T and HeLa cells in the next couple of years. Taken together, these large-scale human PPI networks provided a broad view of whole genome complexomes and invaluable resources for further investigation of protein functions. Nevertheless, just as the completion of two human draft proteomes began the age of proteome discovery, the completion of human draft interactomes reveals only the tip of the iceberg of complex human protein interaction networks. The high-throughput nature of these studies may have compromised the depth and coverage of proteomic analysis. Moreover, studies of the partial interactomes established thus far in HeLa and HEK293T cells were conducted at steady state, thus, they were merely snapshots of highly dynamic PPI networks. The dynamic changes in PPI networks in response to various stimuli and/or under distinct physiological and pathological conditions will be intensively explored in the near future.

To gain a better understanding of important biological processes, function-oriented medium- to large-scale AP-MS studies were conducted with a focus on a group of proteins with similar functions over the past decade (Li et al., 2015a). These studies established protein interaction networks for transcription and RNA processing machineries (Jeronimo et al., 2007), chromatin remodeling complexes (Mak et al., 2010; Sardiu et al., 2008), deubiquitinating enzymes (Sowa et al., 2009), autophagy systems (Behrends et al., 2010), histone deacetylases (Joshi et al., 2013), cyclin-dependent kinases (Xu et al., 2014), chaperones (Taipale et al., 2014), transcription factors (Li et al., 2015b), and tyrosine phosphatases (Li et al., 2016). Similarly, AP-MS studies focusing on signaling pathways, including all of the known proteins or

the core components involved in a given pathway, were also conducted. PPI networks of the tumor necrosis factor-α/nuclear factor-κB (Bouwmeester et al., 2004), insulin-like receptor/target of rapamycin (Glatter et al., 2011), Hippo (Couzens et al., 2013; Hauri et al., 2013; Kwon et al., 2013; Wang et al., 2014), and insulin-like receptor/phosphoinositide 3-kinase/Akt (Vinayagam et al., 2016) pathways have been established. These function-oriented proteomic studies uncovered hundreds to thousands of novel PPIs, provided new insight into these biological processes and pathways, and generated numerous leads for further in-depth functional studies. Functional validation, sometimes coupled with RNA interference screening or other omics-based analyses, could be conducted for proteins of interest to gain further mechanistic insight into these biological process (Kwon et al., 2013; Wang et al., 2014). An excellent example of this type of research is a recent study by Vinayagam et al. (Vinayagam et al., 2016), in which they monitored dynamic insulin-like receptor/phosphoinositide 3-kinase/Akt PPI networks in response to insulin signaling. Combining AP-MS based PPI analysis with RNA interference screening and quantitative phosphoproteomics, they established a comprehensive and dynamic PPI network for insulin signaling and identified protein phosphatase 2A and reptin/pontin chromatin-remodeling complexes as negative and positive regulators of ribosome biogenesis, respectively (Vinayagam et al., 2016).

Because many of these protein families and signaling pathways are involved in human diseases such as cancer, the newly identified interacting proteins may serve as biomarkers or drug targets for disease diagnosis and treatment in the future. For instance, in a recent proteomic study of transcription factor interaction networks, we established spatial specific interactomes of 56 important transcription factors involved in tumorigenesis and identified 2,156 high-confidence interactions (Li et al., 2015b). Combining these results with the Wnt pathway interactomes we established in a parallel study, we discovered that Forkhead box protein K1 (FOXK1) and FOXK2 are potential Dishevelled (DVL)/Wnt pathway regulators (Wang et al., 2015b). We conducted subsequent in-depth biochemical and functional studies *in vitro* and *in vivo* to further elucidate the mechanisms by which these interactions promote tumor proliferation. We showed that FOXK1 and FOXK2 interact directly with DVL proteins, which are crucial Wnt pathway regulators that transduce canonical Wnt signals to the glycogen synthase kinase 3β destruction complex. The interactions among FOXK proteins and DVL proteins positively regulate Wnt/β-catenin signaling by translocating DVLs into the nucleus. More importantly, an immunohistochemical study of hundreds of patient tissue samples confirmed that FOXK1/K2 protein expression levels are elevated in CRC patients and correlate with DVL nuclear localization (Wang et al., 2015b). These results suggested that FOXK1 and FOXK2 are biomarkers and drug targets for CRC.

These PPI networks can be further combined with information from other omics and clinical databases to create a disease-focused network with a hierarchical structure. For instance, by combining the human transcription factor interaction network with multiple knowledge databases, including TCGA database and clinical outcome databases, we created a transcription factor-cancer network and identified Forkhead box protein R2 (FOXR2) as a top-ranked candidate proto-oncogene (Li, 2016). We further recognized that FOXR1 and FOXR2 form stable complexes with Myc and Max, transcriptionally activate a subset of Myc target genes, and subsequently regulate several Myc downstream signaling pathways. In addition, we found that FOXR2 was highly expressed in several breast, lung, and liver cancer cell lines and related patient tumor samples and that reduction of FOXR2 expression in a xenograft model inhibited tumor growth (Li, 2016). Because FOXR2 is only expressed in cancer cell lines and tumor samples, not in healthy tissue (Li, 2016), we speculated that agents that disrupt FOXR2 expression or FOXR2-Myc interaction in adult tissues have side effects that are limited or milder than those of agents that directly target Myc and therefore hold great therapeutic potential.

Taken together, the results of these PPI studies demonstrated cross-talk among different proteins and signaling pathways, and linked many previously unrecognized signaling events together. Novel biomarkers and drug targets can be identified and tested in in-depth mechanistic and preclinical studies, and they may serve as future targets for precision medicine (Figure 2).

EXPLORING INDIVIDUAL PPIS FOR THE UNDERSTANDING OF HUMAN DISEASES

Functional studies of specific proteins of interest are mainstays of biological research. Protein collection, gel separation, Western blotting, and *in vitro*/*in vivo* function validation have made up the workflows of most mechanistic studies over many decades. More recently, omics-based approaches, such as next-generation sequencing and MS, have made possible monitoring of the whole genome and proteome changes upon stimulation. Thus, they are revolutionizing biomedical research by transforming traditional low-throughput hypothesis-driven research into unbiased discovery-driven research. As part of this trend, AP-MS serves as a good example of combining hypothesis- and discovery-driven research. An individual protein or several proteins of interest can be affinity-purified in relevant organisms and cells by researchers familiar with these proteins. Results of AP-MS are usually manually analyzed, and the protein-binding partners potentially functional relevant are selected for validation and in-depth studies. This method has proven to be effective in studying biological processes such as DNA damage signaling path-

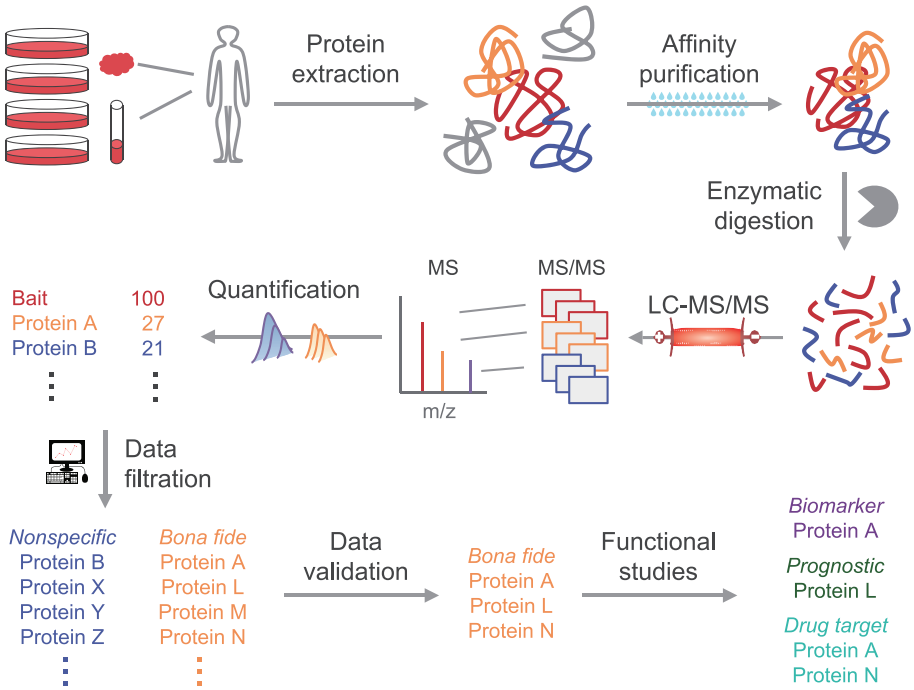

Figure 2 An integrated view of AP-MS-based proteomic workflows. Step 1, proteins are extracted from cells. Proteins of interest (baits) are affinity-purified from cell lysates together with their binding partners (preys) and contaminants. Step 2, the proteins are enzymatically digested into peptides and then separated using LC and electrosprayed into a mass spectrometer. Step 3, the MS are performed. The DDA method is most commonly used. Step 4, databases are searched and spectra are mapped to peptides and proteins. Step 5, post-MS data analysis is performed using different algorithms to distinguish *bona fide* interacting proteins from contaminants. Step 6, data validation, including knowledge PPI database overlapping, co-immunoprecipitation confirmation of bindings, and reciprocal AP/MS validation of a subset of the interactomes. Step 7, in-depth mechanistic studies can be conducted for several proteins potentially functional relevant, to produce biologically meaningful results.

ways for more than a decade, as DNA damage-related proteins often form large protein complexes to execute their functions.

A good example is the AP-MS studies of the breast cancer type 1 susceptibility protein (BRCA1) and the BRCA2. They play pivotal roles in the maintenance of genome stability, a hallmark of cancer cell development. Germline mutations of the human *BRCA1* and *BRCA2* genes account for most familial cases of breast and ovarian cancer. BRCA1 and BRCA2 are the master regulators of the DNA damage response. They initiate cell cycle checkpoint control and DNA repair by forming protein complexes with other proteins involve in DNA damage response and repair. However, how DNA damage signals are transmitted to modulate the repair function of BRCA1/2, and how they are recruited to the DNA damage sites, remained largely elusive a decade ago. Using BRCT domain of BRCA1, a motif that binds phosphorylated proteins (Manke et al., 2003; Yu et al., 2003), as the bait, three research groups performed AP-MS using different tags and labeling strategies. They independently identified the ubiquitin-interacting motif-containing receptor-associated protein 80 (RAP80) as a novel BRCA1 binding protein, which is required for BRCA1-mediated DNA damage responses (Kim et al., 2007; Sobhian et al., 2007; Wang et al., 2007). From there, researchers further identified abraxas/CCDC98 from both BRCT and RAP80 AP-MS results, and found it is also required for proper BRCA1 localization following DNA damage (Liu et al., 2007; Wang et al., 2007). Using RAP80 and CCDC98 as baits, more proteins in this protein complex, including BRCC36, BRE/BRCC45 and NBA1/MERIT40, have been identified (Feng et al., 2009; Shao et al., 2009; Wang et al., 2009). These proteins from a large BRCA1 super-complex, which enable the targeting of BRCA1 to DNA double-strand breaks (Huen et al., 2010). Moreover, AP-MS using a BRCA2 monoclonal antibody identified FLJ21816/LOC79728, which was later named partner and localizer of BRCA2 (PALB2), as a novel BRCA2 interacting protein. PALB2 colocalizes with BRCA2 in nuclear foci, promotes its localization and stability in chromatin and nuclear matrix, and enables its recombinational repair and checkpoint functions (Xia et al., 2006). Reciprocal AP-MS not only identified BRCA2, but also BRCA1, form stable protein complexes with PALB2. This indicates the existence of a BRCA1-PALB2-BRCA2 complex, disruption of which resulted in defective homologous recombination repair and tumor initiation (Sy et al., 2009; Zhang et al., 2009). Taken together, we have gained much new insight into the regulation of DNA damage-responsive pathways on the basis of AP-MS results regarding individual DNA damage-responsive proteins, providing us with a better understanding of the DNA damage response network and the mechanisms of related diseases.

Because this type of studies provides clues about protein functions and regulations for further in-depth mechanistic studies, it has been employed in numerous biomedical investigations. The AP-MS methodology is now well established. To perform AP-MS for individual proteins, overexpression of tagged bait proteins is frequently used, especially in large-scale AP-MS studies. The tagged proteins are usually introduced into cells through transfection or viral infection. Stable cell lines are established for AP, which is performed using epitope tags (Gingras et al., 2007). This approach is technically convenient and does not rely on the use of high-quality antibodies against endogenous proteins, which are often difficult to obtain. Moreover, antibodies against endogenous proteins often pull down many nonspecific cross-reactive binding proteins that are specific to particular antibodies. These cross-reactive binding proteins are impossible to eliminate via bioinformatic analysis (Aebersold and Mann, 2003). Nevertheless, AP-MS using tagged proteins has some drawbacks. For example, overexpression of a given protein may disrupt the assembly of large protein complexes (Gibson et al., 2013), and overexpressed proteins often saturate the AP system and impede the capture of dynamic changes in PPIs in response to biological stimuli (Braun et al., 2006).

For monitoring of weak or dynamic interactions among individual proteins, AP-MS using antibodies against endogenous proteins would be ideal, as this process cause minimal disturbances to the cell system and may prevent overexpression artifacts. Labeling-based MS approaches, such as quantitative immunoprecipitation combined with knockdown method, which couples RNA interference with SILAC, were introduced to resolve the antibody cross-reaction in AP-MS using antibodies against endogenous proteins (Blagoev et al., 2003; Ranish et al., 2003; Selbach and Mann, 2006; Tackett et al., 2005; Trinkle-Mulcahy et al., 2008). The recently developed clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 genome editing technology (Cong et al., 2013; Jinek et al., 2012; Mali et al., 2013) provides an opportunity to further improve this concept. Combining CRISPR /Cas9 gene knockout technology with modified AP-MS protocols, we recently established an endogenous PPI network for neurofibromin, an important tumor suppressor, and identified many novel neurofibromin-binding proteins (Li et al., 2017). Using CRISPR/Cas9-mediated knock-in technology, epitope tags can be introduced into a bait protein at its endogenous locus. This enables researchers to use existing anti-epitope antibodies to perform such endogenous AP-MS studies (Dalvai et al., 2015; Dickinson et al., 2013). For example, using genetically engineered HEK293T cells with FLAG-tag knocked-in, investigators found that a four-protein complex recruited GATOR1 to lysosomes, which is critically important for nutrient-mediated regulation of mammalian target of rapamycin complex 1 activity (Wolfson et al., 2017). These methods do not require high-quality antibodies against endogenous proteins or complicated data-analysis algorithms to eliminate contaminants from AP-MS results. Thus, they hold a great deal of promise regarding future small-scale AP-MS studies for functional explorations in biomedical research.

FUTURE PERSPECTIVES

Hypothesis-driven studies have represented the driving force for biomedical research for almost half a century. Researchers often focus on one biological process and/or answer one specific question. Hypotheses are proposed and tested, and new hypotheses are generated based on the observations. Hypothesis-driven research has proven to be effective and identified molecular mechanisms underlying many human diseases. However, the great success of omics-based approaches to biomedical research has pointed out a new path: discovery-driven research. In it, high-throughput experimental data are collected in an unbiased manner, and conclusions are generated based on these large data sets. We are now in an era of data overflow. The technological advancement in MS analysis in proteomic studies is far exceeding our ability to handle the resulting information properly. The challenges in obtaining, storing, and distributing large amounts of data are gradually being addressed. The major challenge now is how to make sense of this large amount of data and generate new hypotheses that can be tested and verified (Bell et al., 2009).

Our ability to analyze the large amounts of data generated in proteomic studies lags far behind our ability to analyze sequencing data. For instance, proteomic data can be reanalyzed to draw important conclusions (Gavin et al., 2002; Ho et al., 2002; von Mering et al., 2002), especially when they are stored in public repositories such as ProteomeXchange in standardized formats (Vizcaíno et al., 2014). However, many valuable data are still lost owing to the limited number of precursor ions selected for MS/MS fragmentation in traditional DDA mode (Aebersold and Mann, 2016). Recent advances in DIA with full MS2 scans in a given range, which quantify all fragment ion intensities when reference spectra are available, provide a solution for this problem (Collins et al., 2013; Gillet et al., 2012; Reiter et al., 2011). This type of DIA generates much more data than does DDA and provides a panoramic view of all the possible MS/MS spectra but at the same time brings new challenges in data analysis. Recent developments in DIA bioinformatics greatly improved the accuracy and sensitivity of DIA-based data analysis (Teo et al., 2015; Tsou et al., 2015; Wang et al., 2015a) and resulted in biologically

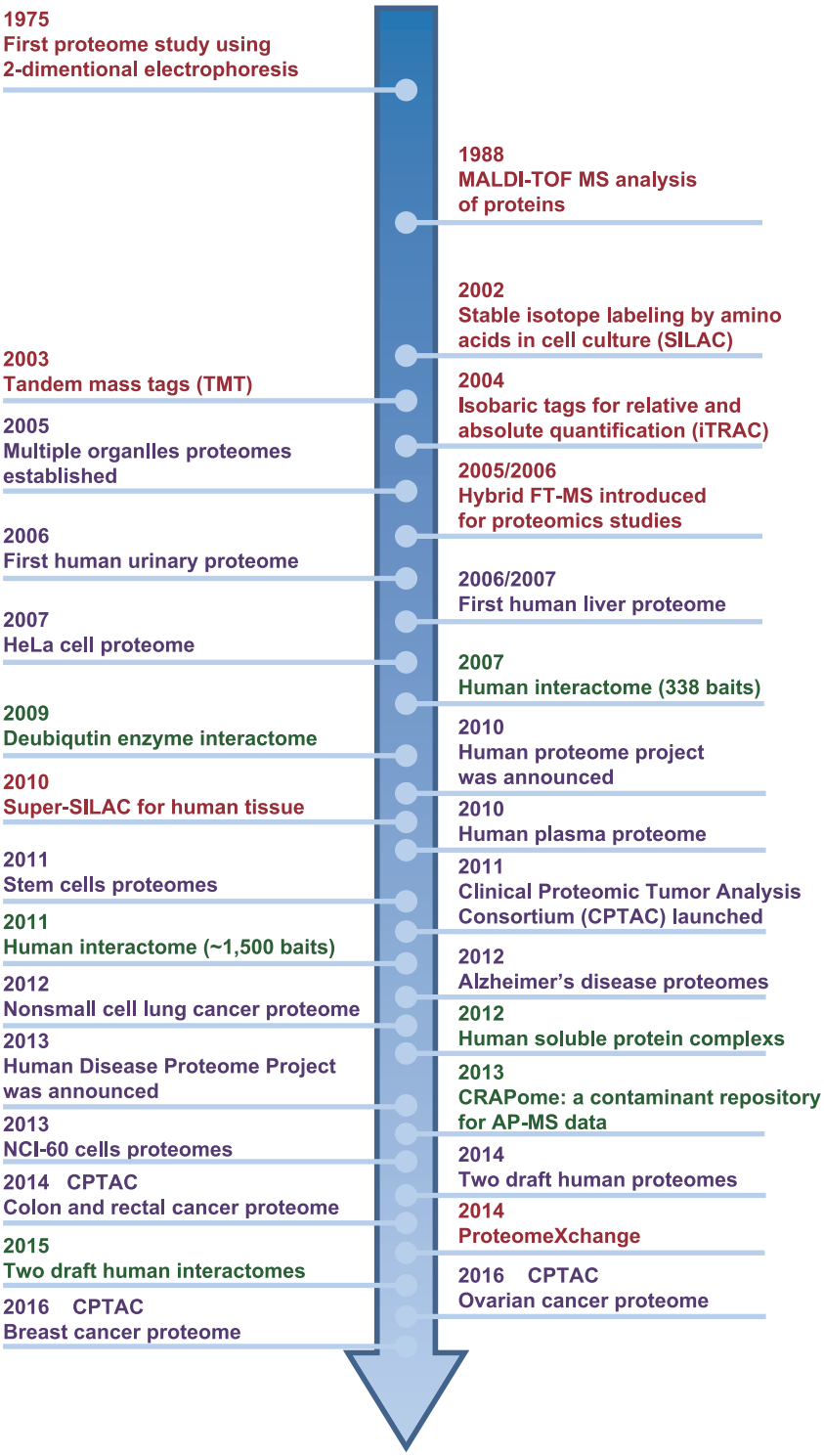

Figure 3 Major events in MS-based biomedical research together with the years of corresponding publications. Red, technical MS advances. Purple, MS-identified human proteomes. Green, AP-MS-identified human interactomes.

meaningful discoveries (Lambert et al., 2013). However, the library of DIA data is far from sufficient to recognize the large number of spectra acquired. Moreover, because each DIA provides accurate MS1 and MS2 label-free quantification in a single experiment, both of which provide unique and irreplaceable information, effectively using all these available information will greatly improve the dynamic range and accuracy of MS data. Many of these challenges in bioinformatic analysis of MS-based proteomic data will be addressed in the near future. However, we anticipate that new challenges will come up with technology advances in this exciting and growing field.

Similar challenges exist for AP-MS data analysis. Knowledge databases containing PPI information are very important to biomedical researchers in generating hypotheses and/or validating observations. Currently, such knowledge databases, including STRING (von Mering et al., 2003), the Biological General Repository for Interaction Datasets (Stark et al., 2006), IntAct (Kerrien et al., 2007), the Database of Interacting Proteins (Xenarios et al., 2000), and the Human Protein Reference Database (Prasad et al., 2009), curate all publicly available PPI data, which were generated across many decades using diverse experimental approaches. Because most high-throughput PPI exploration approaches, such as yeast two-hybrid screening and AP-MS, generate significant amounts of information on nonspecific PPIs, the reliability of the databases listed above is questionable. In a recent study of the endogenous neurofibromin interaction network, more than 50% of previously reported neurofibromin-interacting proteins were found to be potentially nonspecific due to antibody cross-reactions (Li et al., 2017). This indicates the need for establishing a high-quality PPI database with unified quality-associated scores assigned to each individual PPI. The establishment of such a database will represent a leap forward in biomedical research.

Use of function-oriented AP-MS to study a group of related proteins serves as a good example of combining discovery- and hypothesis-driven research. Focusing on specific biological questions, researchers can conduct AP-MS with a group of proteins having related functions, draw conclusions based on the results, and perform validation and in-depth mechanistic and functional studies. This workflow also applies to proteins involved in the same disease based on the existence of disease-related PPI networks (Gandhi et al., 2006), as a disease is usually caused by disruption of one or more related complex molecular processes, and the relationships among these processes are encoded in the interactomes (Menche et al., 2015). Researchers made such an effort a decade ago using a yeast two-hybrid approach. Lim et al. established an interaction network of 54 proteins involved in human inherited ataxias and identified 770 interactions. Moreover, they uncovered several potential regulators of neurodegeneration in animal models (Lim et al., 2006). Unfortunately, in comparing the well-established and rapidly growing number of new disease proteomes, studies of disease-oriented PPI networks are time-consuming. Nevertheless, systematically establishing interaction networks of all proteins involved in the same disease may reveal novel regulators and mechanisms of the disease and therefore shed light on disease diagnosis and prognosis. Proteogenomic concepts should be adopted for this type of research. A potential starting point is diseases with relatively clear genetic backgrounds, such as inherited genetic disorders, with eventual expansion to complex diseases such as cancers and cardiovascular diseases.

The Human Genome Project (Schmutz et al., 2004) took 13 years of collaboration among several countries to map the whole genomes of a few individuals. Now, the entire human genome can be sequenced in a few days, and thousands of diagnostic genomic tests are available to the public. We have every reason to expect MS-based proteomics to follow the same path. The rapid development of MS proteomics over the past decade gives us confidence that it will eventually reach throughput and sensitivity comparable with those of genomic-based technologies (Figure 3). MS proteomics will revolutionize mechanistic studies of diseases, as it will provide all protein information, including protein abundance, modification, and interactions, at once. Therefore, it will be used routinely in biomedical research and disease diagnosis in the near future just as sequencing is today.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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