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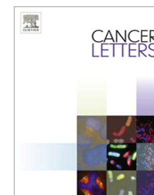

Mini-review

Cancer metabolism and mass spectrometry-based proteomics

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ABSTRACT

Cancer metabolism has been extensively investigated by various tools, and the fact of diverse metabolic reprogramming in cancer cells has been gradually unveiled. In this review, we discuss some contributions in cancer metabolism by general proteomic analysis and post-translational modification analysis using mass spectrometry (MS) technique. Instead of following one or several metabolic enzymes/pathways, the current MS approach can quickly identify a large number of proteins and compare their expression levels in different samples, providing a potentially comprehensive picture of cancer metabolism. The MS analyses from pancreatic cancer cells support a hypothesis that hypoxia promotes cells in solid tumor to reprogram metabolic pathways in order to minimize the oxygen consumption. The oxidative stress in pancreatic cancer cells is lower than that in normal duct cells, and the cancer cells adaptively express less antioxidant proteins, contrary to claims that oxidative stress is higher in cancer cells. Separately, the MS analyses confirm that pyruvate kinase isoform 2 (PKM2) can be detected in both cancer and normal cells, disagreeing with report that tumor cells express exclusively PKM2. In addition, MS analyses from pancreatic cancer cells demonstrate that lactate dehydrogenase-B is significantly upregulated in pancreatic cancer cells, whereas previous reports show that lactate dehydrogenase-A is overexpressed and is responsible for lactate production in cancer cells. Lastly, the result from MS analysis suggests that the glutaminolysis in pancreatic cancer cells is different from that observed in glioblastoma cells.

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1. Introduction

Today, mass spectrometry (MS) is used routinely for large-scale protein identification and global profiling of post-translational modifications (PTMs) from complex biological mixtures. The progress of this powerful proteomic tool has been driven by the development of new technologies for peptide/protein separation and sustaining innovations in high scan rate, high sensitivity and high mass accuracy mass spectrometers. Unquestionably, the rapid advance of MS technique is greatly assisted by the complete sequencing of many genomes and improvement in computer industries [1–4].

MS-based proteomic research is mainly focused on qualitative analysis, quantitative analysis and bioinformatic analysis. The objective of qualitative analysis is to identify as many as possible proteins or PTMs in the sample based on acquired MS spectra, and the "shotgun" approach using liquid chromatography–coupled tandem mass spectrometry (LC–MS/MS) is typically performed (Figs. 1 and 2). There are 20,059 Ensembl protein-coding human genes, and approximately 65–70% of the expected proteins have been confidently identified from various MS analysis to date. Deep proteomic discovery experiments are still performed to find the remaining 30–35% of proteins [5]. Collision-induced dissociation (CID), higher energy C-trap dissociation (HCD) and electron-transfer dissociation (ETD) are the most widely used techniques to fragment peptide ions in a mass spectrometer and have proven to be extremely useful for amino acid sequence assignment and for PTMs studies [6]. Currently, MS-based analysis can identify approximately 10,000 proteins from human cell lines in a single proteome discovery project [7–10]. In addition, more than 10,000 phosphorylation sites and more than 3000 acetylation sites can be identified from cells by MS analysis [11–14]. To quantitatively characterize and compare two or more proteomes by MS, a variety of methods involving the incorporation of stable isotope labels, such as isotope coded affinity tag (ICAT), isotope tags for relative and absolute quantitation (iTRAQ), and stable isotope labeling by amino acids in cell culture (SILAC) have been developed [6,15]. Notably, alternative label-free quantitation approaches, either by measuring and comparing the MS signal intensity of peptide precursor ions or by counting and comparing the number of matched fragmentation spectra (MS2 spectra) of a given protein, have gained increasing popularity over the past several years [16–18]. Separately, selected reaction monitoring (SRM) technique has been developed as a targeted MS technique for the detection and quantification of specific, predetermined analytes with known

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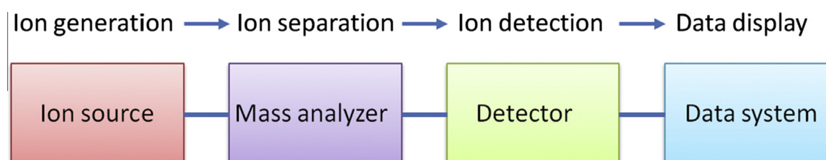

Fig. 1. Basics of mass spectrometry. Mass spectrometry (MS) measures the mass of molecule by measuring the mass-to-charge ratio (m/z). A typical mass spectrometer includes ion source, mass analyzer, detector and data system. The mass spectrometer is under high vacuum to allow unhindered movement of ions. The ion source ionizes sample and generates gas phase ions. Since only charged (positive or negative) molecules can be detected by MS, soft ionization is needed to transfer non-volatile peptide from atmospheric or solvated condition to high vacuum state. The matrix-assisted laser desorption/ionization (MALDI) and liquid chromatography (LC)-coupled electrospray ionization (ESI) are the two mostly used methods to ionize biological samples. The mass analyzer separates peptide ions according to individual m/z value. The common mass analyzers are quadrupoles, ion trap, time-of-flight (TOF), Orbitrap and ion cyclotron resonance (ICR). The quadrupoles and ion trap have relatively poor mass accuracy, and Orbitrap and ICR have relatively higher mass accuracy. The detector monitors ion current, amplifies it and transmits signal to data system. The common detectors are photomultiplier, electron multiplier and micro-channel plate. The data system not only converts the signal into a readable or graphic display, but also controls the operation of mass spectrometer. Since the measured mass has error ranging from several parts per million (ppm) to several hundred ppm depending on mass analyzer installed, obtaining the mass of a peptide is not enough to distinguish it from other peptides that have similar mass. As a result, tandem mass spectrometry (MS/MS) technique is developed to elucidate the structure of the peptide. For MS/MS analysis, the mass spectrometer first measures the m/z of the peptide and records the information in primary ion spectrum (MS1 spectrum). Then the mass spectrometer isolates and fragments the peptide to multiple daughter ions. The m/z values of these daughter ions are recorded in fragmentation spectrum (MS2 spectrum) that is unique. Generally, both MS1 and MS2 are needed to confirm the identity of a peptide. Collision-induced dissociation (CID), higher energy C-trap dissociation (HCD) and electron-transfer dissociation (ETD) are the most widely used techniques to fragment peptide ions in a mass spectrometer.

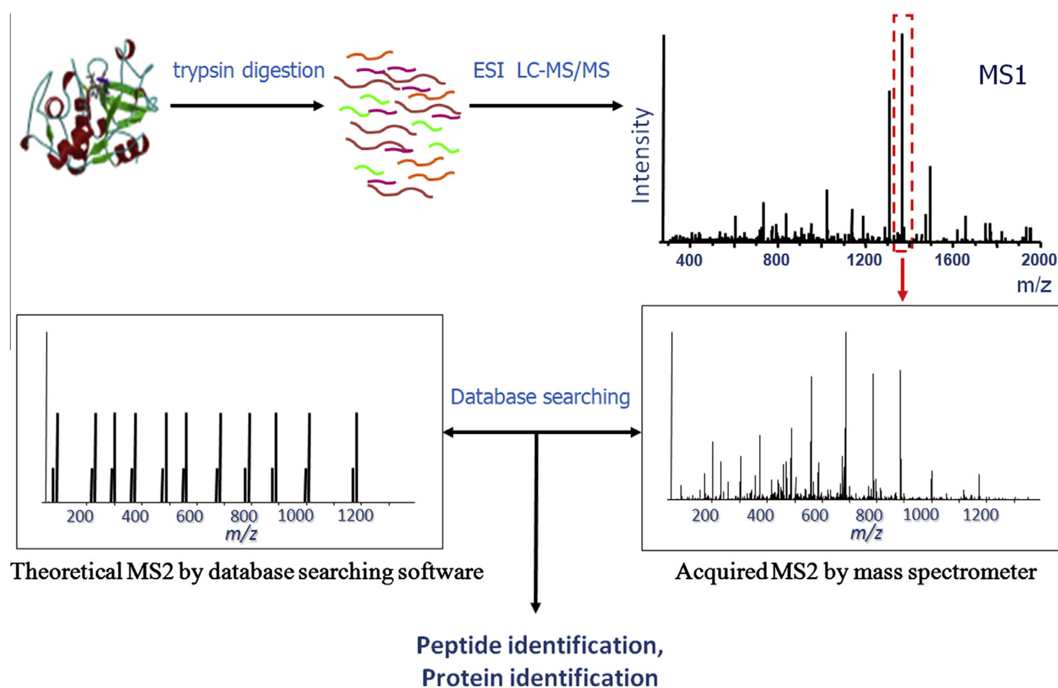

Fig. 2. Typical mass spectrometry-based proteomics workflow. Shotgun proteomics refers to the use of bottom-up proteomics technique in identifying proteins in complex mixtures using liquid chromatography-coupled tandem mass spectrometry (LC–MS/MS). Proteins are digested by trypsin to generate small tryptic peptides that are within the optimum mass range for MS measurement. The peptide mixture is then loaded directly onto a microcapillary C18 column and the peptides are separated by hydrophobicity. As the peptides elute from the column, they are ionized by electrospray ionization (ESI) and their m/z values are recorded by the first stage of tandem mass spectrometry as MS1 spectra. The selected ions undergo collision-induced dissociation (CID) and the m/z values of charged fragments are recorded by the second stage of tandem mass spectrometry as MS2 spectra. The MS2 spectra are used to identify the proteins from which they derive by searching against a sequence database with commercially available software such as SEQUEST and MASCOT.

fragmentation properties in complex backgrounds [19,20]. Lastly, high throughput shotgun proteomics faces challenges with respect to the analysis and interpretation of experimental data. Consequently, a lot of bioinformatic tools, such as Protein Knowledgebase (http://www.uniprot.org), Gene Ontology Analysis (http://www.geneontology.org), DAVID Bioinformatics Resources (http://david.abcc.ncifcrf.gov) and Ingenuity Pathway Analysis (http://www.ingenuity.com), have been developed in order to annotate the biological function of identified proteins, to map protein–protein interactions, or to find biomarkers relevant to diseases [21–23]. The ultimate goal of bioinformatic analysis is to help MS practitioners build a hypothesis that can reasonably and maximally explain the acquired data.

The importance of metabolic reprogramming in cancer is being increasingly recognized, and multiple drugs targeting metabolic enzymes for cancer therapy have been developed [24–27]. In the past decade, various MS-based approaches have been applied to investigate the proteomes of cancer and normal samples from tissues, cell lines and body fluid, with the goals of dissecting the abnormal metabolism and signaling pathways underlying oncogenesis. Certainly, discovery of the differentially expressed proteins or PTMs will facilitate the development of new therapies and drugs, targeting the specific needs of cancer cells [28–32]. Additionally, MS has been used for large scale metabolite profiling in cancer cells, and research on cancer metabolomics has been reviewed elsewhere [33–39]. In this mini review, we discuss the

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