

## Review Article

# The Application of SELDI-TOF-MS in Clinical Diagnosis of Cancers

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Received 20 December 2010; Accepted 30 March 2011

Academic Editor: Vincent C. O. Njar

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Cancer diagnosis is important, and the early diagnosis of cancers could predict a more successful treatment. The proteomic studies emerged to be useful in combined analyses of samples from patients and provide more accurate diagnosis when compared to the single-factor-based diagnosis. In recent years, cancer detection with surface-enhanced laser desorption/ionization time of flight mass spectrometry (SELDI-TOF MS) is flourishing and brought significant progress in this area. This paper summarizes some recent results with this technique for cancer diagnosis.

## 1. Introduction

Cancer diagnosis is important, and the early diagnosis of cancers could predict a more successful treatment. The accurate diagnosis of cancers before the appearance of symptoms often relies on the identification of reliable biomarkers. Further, these biomarkers reflecting the progression of cancers suggest the etiology of the disease. Proteomics technology has emerged to be important tools in cancer diagnosis and evaluation tools during treatment through the analyses of changes in cancer biomarkers. The fact that people have identified diverse biomarkers during the development and progression of different cancers suggested that the specificity and abundance of many small proteins could reflect the current state of cancer progression, and even predict the treatment efficacy. From serum, saliva, urine, and so forth, people could acquire the complete proteome that reflect the dynamic proteomics of the patients with high accuracy; and proteomic analyses permit the combined comparison of several biomarkers at the same time, which could finally bring convincing results. This included two-dimensional gel electrophoresis (2-DE), one- or two-dimensional liquid

chromatographic (LC-MS), and surface-enhanced laser desorption/ionization time of flight mass spectrometry (SELDI-TOF MS). In the present paper we review the progresses achieved in using SELDI-TOF MS technology for cancer biomarker profiling and detection.

## 2. Introduction to SELDI-TOF MS

The SELDI-TOF MS technique was firstly introduced in 1993 [1] and was commercialized by Ciphergen Biosystems in 1997 as the ProteinChip system. SELDI-TOF-MS is one type of variation of matrix-assisted laser desorption/ionization (MALDI) that uses a target modified to reach biochemical affinity with the sample proteins. The differences between the two techniques are the following. In MALDI, the sample is mixed with the matrix molecule in solution, and a small amount of the mixture was deposited on a surface to dry. This made the sample and matrix cocrystallized after the solvent evaporated. On the other hand, in SELDI, the mixture is spotted on a surface modified with a chemical functionality such as binding affinity. Without being dried, some proteins in the samples would bind to the modified

surface, while the others were washed off. Then the matrix is applied to the surface for crystallization with the sample peptides. In the binding and washing off steps the surface-bound proteins are left for analyses. Samples spotted on an SELDI surface were typically analyzed with time-of-flight mass spectrometry (TOF-MS) [2]. A laser-ionized peptides from crystals of the sample and matrix mixture. These ions were then accelerated through an electric field and down into the flight tube. Finally, the detector would measure ions as they reach the end of the tube (Figure 1). The mass-to-charge ratio of each ion could be determined from the length of the tube, the kinetic energy given to ions by the electric field, and the time taken to travel the length of the tube. Some surfaces that were normally adopted include CM10 (weak-positive ion exchange), H50 (hydrophobic surface, similar to C6-C12 reverse phase chromatography), IMAC30 (metal-binding surface), and Q10 (strong anion exchanger). Surfaces can also be modified or functionalized with antibodies, other proteins with proper binding properties, or even DNA.

### 3. Body Fluids as Important SELDI-TOF MS Samples

One of the key features of SELDI-TOF MS is the little requirement of sample purification or protein separations before the MS analyses. With high sensitivity to low-molecular-weight proteins (less than 15 kDa), SELDI-TOF MS could detect some biomarkers that were neglected in other proteomic analyses such as 2D-gels [3, 4]. In finding samples for SELDI-TOF MS analysis, both tissue extracts and body fluids could be used. In past studies, the analyzed body fluids include plasma, serum, urine, saliva, amniotic fluid, cerebrospinal liquid, bronchoalveolar wash out, tears, and nipple aspirate fluid [5–23]. Among these choices, serum, urine, saliva, and plasma were most widely used.

The challenge that biomarker proteins only take a very small proportion in total plasma proteins—less than one percent suggested that MS is more suitable in cancer detection in compared to other less sensitive approaches [24]. Moreover, the levels of proteins could vary according to the environmental stress, codiseased disorders or previous drug treatments [24, 25]. Sometimes, the proteins were modified or cleaved by enzymes, which further decreased the amount of biomarkers for detection in body fluids. All these difficulties suggested that cancer detection should adopt SELDI-TOF MS technique with high sensitivity and without the need of previous protein purification from samples. Consistently, it was showed that the highly abundant proteins in the serum such as albumin and immunoglobulin could be well separated from potential markers without causing any inference [16, 26–29].

### 4. Cancer Diagnosis

Many types of cancers could be and have been diagnosed with SELDI-TOF MS technology. It is possible to read the different peaks in samples from control and patients, as shown in Figure 2. In the paragraphs below, we selected

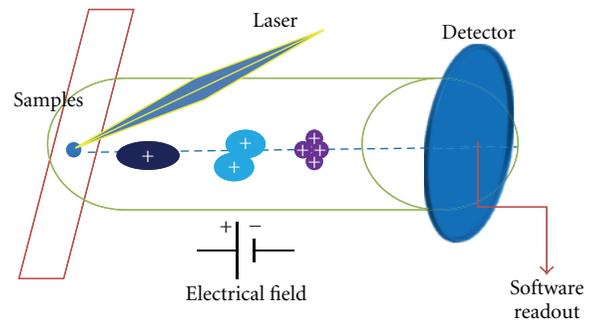


FIGURE 1: After the samples were dried, a laser-ionized peptides from crystals of the sample and matrix mixture. Then, these ions were accelerated through an external electric field and down into the flight tube. Finally, the detector would measure ions as they reach the end of the tube with software readout the data.

ovarian cancer, breast cancer, prostate cancer, and hepatocellular cancer as examples showing how the new technique promoted the diagnosis of these cancers.

**4.1. Ovarian Cancer.** It was found that early diagnosed (phase I) ovarian cancer patients have the 5-year survival rates more than 90%, which is 35% in most middle-late phase cases [30, 31]. Some studies tried to diagnose phase I patients accurately. For instance, one study adopted C16 surface chips with SELDI-TOF MS in analyzing 50 patient cases and found a different pattern of proteome including five peaks at 534, 989, 2111, 2251, and 2465, respectively, [31, 32]. In most of these studies, the method could reach diagnosis accuracy, sensitivity, and specificity of more than 99%, especially when combined with improved statistical methods [33–40]. Taken together, SELDI-TOF MS could be an important and very accurate tool in diagnosing ovarian cancer patients, both in early and advanced stages.

**4.2. Breast Cancer.** X-ray examination was now routinely adopted for women aged more than 40 years old however, the accuracy is only around 50%. There were some available biomarkers in serum for breast cancer diagnosis, such as CA15.3, but with low sensitivity (23%) and specificity (69%) [41, 42]. In one study that combined IMAC-Ni<sup>2+</sup> chip with SELDI-TOF MS, the authors showed three protein spectrum peaks at 4.3, 8.1, and 8.92 kDa, respectively, combined analyses with the three peaks in 169 cases (103 patient cases) and showed the diagnosis sensitivity 93% and specificity 96% [43]. In other studies, many other potential biomarkers have been identified, and reached high accuracy in diagnosis [44–55], and combined analyses of these biomarkers could further improve the sensitivity and specificity.

**4.3. Prostate Cancer.** Prostate-specific antigen (PSA) has been widely used in prostate cancer diagnosis with relatively high sensitivity but quite low specificity [56, 57] 95% and 18%, respectively, as shown in one previous study [58]. Many studies have adopted SELDI-TOF MS to find better biomarker for early prostate cancer diagnosis [59–68]. One

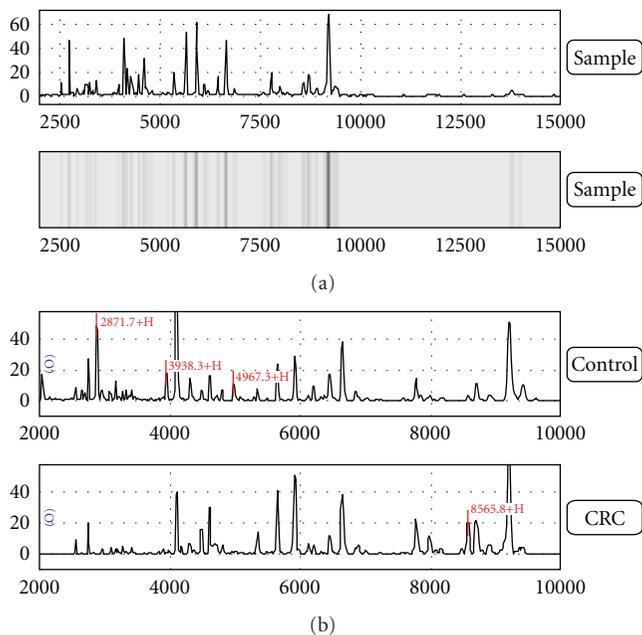


FIGURE 2: Samples from control and colorectal cancer patients showed different peaks in proteomics spectrum. Some changes were highlighted.

study compared serum samples from prostate cancer patients and patients with other prostate diseases for SELDI-TOF MS analyses; they found several biomarkers including PC1, PC2, and PC3, with higher sensitivity when compared to PSA-based diagnosis in the study involved in more than 300 cases [69]. The serum-based proteomic analysis would become one of the major diagnosis tools for prostate cancer in the future.

**4.4. Hepatocellular Cancer.** Hepatocellular cancer (HCC) is the most common primary malignant tumor of the liver. Primary liver cancer accounts for less than 1% of all cancers in states, however, in past decades, this increased due to a large pool of people with longstanding hepatitis C virus infection. This is even worse in China and many developing countries. The detection of HCC could be very difficult, as most patients onset without any symptoms. Ultrasound detection and alpha-fetoprotein (AFP) in the serum were used in past studies [71, 72]. However, it should be noted that serum AFP levels were normal in 40% patients with <2 cm (in diameter) hepatocellular carcinoma and in 28% of those with tumors 2 to 5 cm in diameter. Additionally, not all hepatocellular carcinomas secrete AFP such as the Fibrolamellar type. The AFP levels could also be elevated in pregnancy, other gonadal originated tumors, and even in acute or chronic liver diseases (CLD) without tumor. All of these weakened the sensitivity and specificity of AFP as serum biomarkers for HCC.

SELDI-TOF MS have been adopted to find new biomarkers for HCC diagnosis [71, 73–82]. In another study, the authors adopted the multidimensional separated statistics in analyzing the proteomics data and showed diagnosis

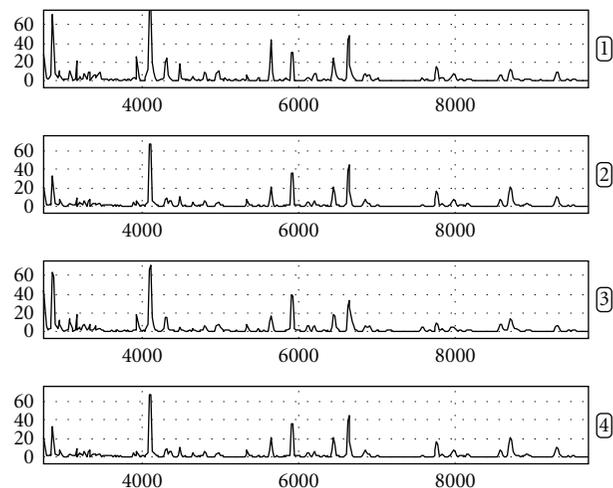


FIGURE 3: This represented the reproducibility of four separate analyses from the healthy controls of blood type O, suggesting the high reliability of SELDI-TOF MS in serum sample analyses [70].

specificity of 90% and sensitivity of 92% in separating HCC out of CLD, which could not be reached with AFP examination [83]. More interestingly, their works showed the proteomics between subtypes of HCC: the progressive one and the metastasis one. All these data could provide new hopes for accurate and early detection of HCC in patients or people living in areas with hepatitis B and C virus infection.

It should be noted that in practice, the combined use of several potential biomarkers could greatly increase the specificity and sensitivity of cancer diagnosis [46, 84–88]. It is now convenient to set up the diagnostic tree with software, and the diagnosis automatically follows. These selected combinations could be considered as a group of biomarkers representing the etiology of cancer in given population, which might provide some rationale bases for therapeutic developments.

## 5. Summary

In this paper, we briefly summarized the recent progresses achieved in cancer detection and diagnosis with SELDI-TOF MS technique. The use of body fluids and tissue extracts with low proteins content as samples in this technology is superior to many other available proteomic approaches. Moreover, SELDI-TOF MS is very sensitive and reliable in repeated tests (Figure 3) [70]. It should also be noted that SELDI-TOF-MS could also contribute to the ongoing human proteome studies, as proposed for the total proteins in the serum [2, 29, 89]. When combined with radiological data, this could finally bring patients new hopes in the early detection of the tumors inside even before the onset of symptoms. For instance, the detection of specific changes in one protein might point out the potential regions of cancer genesis and, therefore, suggest the regions of interest for radiologist; also, when unknown tissues were identified in the radiological report, the accurate SELDI-TOF-MS could be used to verify the existence of a tumor. We believe that SELDI-TOF-MS

would become one of the most powerful tools in early cancer diagnosis in coming days.

## Acknowledgments

The work was funded by Zhejiang Medicine, Health, and Science Grant no. 2010KYB127, Educational Commission of Zhejiang Province Grant no. Y201016269, Science and Technology Planning Project of Hangzhou 20100633B13, and Zhejiang Gong Yi Xing Technology Application Project Grant no. 2011C33SA810001. The author also thanks the Department of Laboratory Medicine, the Affiliated Taizhou Municipal Hospital and Taizhou Medical College for supports.

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