Exp Oncol 2006
28, 4, 282–287

Experimental ONCOLOGY

ESTABLISHMENT OF SERUM PROTEIN PATTERN FOR SCREENING COLORECTAL CANCER USING SELDI-TOF-MS

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Aim: **The purpose of this study is to develop a proteomic pattern for distinguishing individuals with colorectal cancer from healthy controls and monitoring micrometastasis using SELDI-TOF-MS.** ***Methods:*** **A training set consisting of 63 patients with colorectal cancer, 20 patients with benign colorectal diseases and 26 healthy volunteers was used to develop a proteomic model that discriminated colorectal cancer effectively. The sensitivity and specificity of this model was validated by an independent test set. To explore serum proteins changed after operation, the protein profiles of 31 postoperative patients were compared with those of preoperative patients. We also analyzed protein profiles of patients with and without metastasis to monitor micrometastasis.** ***Results:*** **Our study yielded a four-peak model (m/z: 3191.5, 3262.9, 3396.3 and 5334.4) that discriminated cancer from non-cancer samples with sensitivity of 90.3% and specificity of 95.7%. This model was validated in the test set with sensitivity of 87.5% and specificity of 93.8% which was significantly better than the combination use of CEA, CA199 and CA242 (sensitivity 62.4%) for early detection of colorectal cancer. Two peaks (m/z: 2753.8 and 4172.4) were found down-regulated in postoperative samples comparing with preoperative samples. We also detected two proteins (m/z: 9184.4 and 9340.9) that can discriminate patients with primary colorectal cancer from metastatic colorectal cancer.** ***Conclusions:*** **The four-peak model and two peaks (m/z: 2753.8 and 4172.4) detected in this study have the potential for assistance in diagnostics and therapeutic strategies in colorectal cancer and the two proteins (m/z: 9184.4 and 9340.9) were effective biomarkers for monitoring micrometastasis.**

Key Words: **SELDI-TOF, proteomics, colorectal cancer, biomarker, metastasis.**

Colorectal cancer is the fourth most common malignancy in the world, accounting for about 10% of all cancer deaths every year. If patients were diagnosed in the early stage, the overall five-year survival rate can be around 90%. However, about in 35% of cases tumors are not detected until they have invaded the surrounding tissue or metastasized to distant sites. The relative survival rate of such patients is less than 40% [1, 2]. Thus, discovery of specific tumor markers for early diagnosis is of importance for survival rate and prognosis.

Non-invasive methods for colorectal cancer diagnosis mainly include fecal occult blood testing, fecal biochemistry and immunology testing, detection of serum tumor markers and so on [3–5]. All these approaches are neither sensitive nor specific enough for use as the sole screening method for early cancer detection. Novel gene technology, such as microarray and DNA chip, can identify and quantitative mRNA with high sensitivity on a global scale [6, 7]. However, it has been shown that there is no direct correlation between mRNA and protein expression level *in vivo* because of post-transcriptional regulations and post-translational modifications occured in protein expression and synthesis. The mRNA/protein correlation coefficients are only 0.4–0.5 and mRNA cannot accurately represent the quantity of protein which is the true executant of gene function [8–10]. Therefore, more extensive and effective tests are desirable for diagnosis of primary cancer.

National Cancer Institute (NCI) gets a conclusion by clinical experiments: SELDI-TOF-MS is the most promising technology for early detection of cancer [11]. SELDI-TOF mass spectrometry technology is potentially an important tool for the rapid identification of cancer specific biomarkers and proteomic patterns in the proteomes of both tissue and body fluids, especially suitable for serum analysis which contains abundant low molecular weight and low-abundance proteins that carry important diagnostic information but exist below the detection limits of any conventional testing. An advantage of this technology is its ability to simultaneously analyze the whole proteome so that correlated proteins altered in expression can be identified in a single experiment. This makes it possible to combine several protein markers together to form a pattern with higher sensitivity and specificity in the detection and monitoring of cancer.

The aim of this study was to compare serum proteomic profiles between patients with colorectal cancer, benign colorectal disease and healthy controls to discover colorectal cancer-specific biomarker proteins, and to validate these biomarkers with an independent sample set. In addition, protein profiles of patients with colorectal cancer before and after operation were also analyzed.

MATERIALS AND METHODS

Patients and controls. Two independent serum sample sets were analyzed for their protein profiles. The training set consisted of samples from 63 patients

Received: November 8, 2006.

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Abbreviations used: CA199 – carbohydrate antigen 199; CA242 – carbohydrate antigen 242; CEA – carcinoembryonic antigen; SELDI-TOF-MS – surface-enhanced laser desorption/ionization time-of-flight mass spectrometry.

with colorectal cancer (Dukes'A, n = 14, Dukes'B, n = 19, Dukes'C, n = 17, Dukes'D, n = 13), 20 patients with benign colorectal diseases and 26 healthy volunteers. The test set consisted of samples from 48 patients with colorectal cancer (Dukes'A, n = 10, Dukes'B, n = 15, Dukes'C, n = 14, Dukes'D, n = 9), 18 patients with benign colorectal diseases and 14 healthy volunteers. The mean age of cancer patients was 56.7 ± 7.3 years (range 49–75 years) while the mean age of control group was 54.2 ± 3.5 years (range 46–69 years). There was no statistically significant difference in the ages between the two groups ($P > 0.05$). Additional 31 postoperative patients with colorectal cancer were also analyzed. All the serum samples were examined in the laboratory to eliminate diseases influenced content of proteins, such as liver disease. The study was performed after approval by our institute Human Investigations Committee and consent of all the patients and healthy volunteers.

Samples. 5 ml of peripheral blood were collected from the cancer patients and healthy subjects. All the samples were collected before operation and any treatment. For the 31 postoperative patients, blood samples were collected at the 14th day after operation. Each sample was placed at 4 °C for 2 h and was centrifuged at 3000 r/min for 10 min to remove cellular components. Serum samples were collected, aliquoted and kept frozen at –80 °C until use. CEA, CA199, CA242 levels were examined previously.

SELDI analysis. Four types of chip (hydrophobic chip, strong anion exchanger chip, weak cation exchanger chip and immobilized metal anion chip) were tested to determine which could provide the best serum profiles. After evaluation, the weak cation exchanger (WCX) Protein Chip which contains anionic carboxylate groups that bind positively charged proteins in serum was selected for our study.

Serum samples were denatured by adding 20 µl U9 (9 M urea, 2% CHAPS, 50 mM Tris-HCl, pH = 9.0) to 10 µl serum, then adding 360 µl binding buffer. Subsequently, 150 µl denatured samples was applied on Protein Chip which had previously been activated with 10 mM HCl and equilibrated with binding buffer (100 mM ammonium acetate) according to the manufacturer's instructions. After the samples were allowed to incubate for 60 min on a platform shaker, the array was washed twice with 200 µl binding buffer for 5 min, followed by two quick rinses with HEPES solution. Before SELDI analysis, 0.5 µl of a saturated SPA solution (sinapinic acid in 50% aqueous acetonitrile and 0.5% trifluoroacetic acid) was applied onto each chip array twice, allowing the array surface to air-dry between each SPA application. Chips were placed on the Protein Biological System II mass spectrometer reader and time-of-flight spectra were generated by averaging 60 laser shots collected in the positive mode at laser intensity 165 and detector sensitivity 8. Mass accuracy was calibrated on the day of measurements using the All-in-one peptide molecular mass standard.

The reproducibility of SELDI spectra, that is, mass location and intensity from array to array on a single chip (intra-assay) and between chips (interassay), was determined using the pooled normal serum quality control (QC) sample. We compared the average intensity of all peaks in the range of 2000–30000 Da observed on spectra and calculated the coefficient of variance. The intra-assay analyses were performed in quadruplicate, and the inter-assay analyses were performed on three different days.

Statistical analysis. Peak detection was performed using Ciphergen ProteinChip software versions 3.2. The mass range from 2000 to 30000 Da was selected. We focused on this region to eliminate low-mass ($m/z < 2000$) and low-intensity peaks ($m/z > 30000$). Peak detection involved (*a*) baseline subtraction, (*b*) mass accuracy calibration and (*c*) automatic peak detection. Using Biomarker Wizard (BMW) software, biomarkers were generated which represented consistent protein peak sets across multiple spectra. Next, Biomarker Patterns software (BPS) was used to construct the decision tree from the BMW files. The value of the candidate biomarkers in detecting colorectal cancer from non-cancer controls was evaluated by Mann — Whitney *U* test. Mean spectra generated from preoperative and postoperative groups, patients with primary colorectal cancer and metastatic colorectal cancer were compared using Students *t*-test.

Serum CEA, CA199 and CA242 quantification. Serum CEA, CA199 and CA242 were quantified using an electrochemiluminiscence immunoassay on a Modular analytics E170 analyser. The cut-off value of 5 ng/mL, 35 KU/L and 20 KU/L were employed for CEA, CA199 and CA242 respectively. All statistical analyses for these data were performed with *SPSS* software.

RESULTS

Reproducibility. The reproducibility of SELDI mass spectra was successfully testified using the quality control (QC) samples. The intra- and inter-assay coefficients of variance for peak location were 0.04 and 0.05%, and the intra- and inter-assay coefficients of variance for normalized intensity (peak height or relative concentration) were respectively 11 and 14%. There was little variation with day-to-day sampling and instrumentation. The acceptable intra- and inter-assay variations of this method have allowed us to obtain a reliable result in this study.

Cancer-specific biomarkers detection and selectivity. A total of 127 peaks were identified in the m/z region of 2000–30 000 from SELDI spectra of training set. Using Biomarker Wizard software, we compared the spectra generated from cancer group with corresponding spectra generated from control group. This comparison yielded 26 differential peaks (Table 1). Among these, 4 peaks were chose to form a model that could discriminate colorectal cancer patients from control group effectively. The 4 peaks corresponded to m/z ratios of 3191.5, 3262.9, 3396.3 and 5334.4

(Table 2, Fig. 1). All the 4 peaks were up-regulated in the group of patients with colorectal cancer ($P < 0.01$). The sensitivity and specificity of this model was respectively 90.3 and 95.7%. A blind test set consisted of 48 patients with colorectal cancer, 18 patients with benign colorectal neoplasia and 14 healthy volunteers. In our study, correctly classification was achieved in 30 of 32 controls and 42 of 48 cancer patients, including 8 of 10 Duke'A patients.

Table 1. Differently expressed proteins in serum of colorectal cancer group and control group

Mass-charge ratio of protein (m/z)	*P* value	The average intensity of protein peak	
		Colorectal cancer group	Control group
2753.8	0.00004	31.11608654	12.1590982
9289.3	0.00003	24.35909	13.14588
5334.4*	0.00002	22.73111	6.084794
3191.5*	0.0009	7.725975	2.0018
4645.9	0.0009	11.21654	5.426459
3262.9*	0.001	10.033386	3.291793
4172.4	0.001	19.398129	5.92417203
5803.7	0.001	7.97111	1.900566
14123.7	0.001	2.656011	4.71362
14023.8	0.001	4.604952	7.730591
28024.4	0.001	8.792696	15.22274
2963.9	0.002	7.322281	1.991357
5904.1	0.002	42.15694	14.6972
2949.8	0.002	19.81355	5.610585
5831.7	0.002	6.03706	2.348323
3396.3*	0.002	23.88053	8.67945
28858.68	0.002	1.792869	3.191014
13742.1	0.003	2.209401	3.782254
5263.0	0.005	5.592539	1.753355
4671.9	0.007	4.737961	2.475495
5745.4	0.01	2.134776	1.351598
2899.9	0.01	3.988201	0.886663
7971.9	0.01	15.78563	10.27681
15841.9	0.02	13.43144	7.96911
11795.6	0.02	5.15713	1.362526
23369.7	0.04	6.67954	8.803534

The proteomic spectra indicated the average intensity of differently expressed proteins in two groups. The four peaks that constructed diagnostic model were marked by * sign.

Table 2. Differently expressed proteins in blood serum of preoperative and postoperative groups

Mass-charge ratio of protein (m/z)	*P* value	The average intensity of protein peak	
		Preoperative group	Postoperative group
2753.8	0.00005	31.21516847	11.2172390
4172.4	0.001	20.0139783	5.78351392

CA199, CA242 and CEA levels were available for all the cases in training set and test set. We found that combination of these three markers had the sensitivity of 62.4% and specificity of 86.2% for distinguishing colorectal cancer from controls. Obviously, the proteomic model generated from our study had higher sensitivity than the combination of CA199, CA242 and CEA for diagnosing colorectal cancer ($P < 0.005$) though the specificity had no statistic difference.

Different preoperative and postoperative markers in colorectal cancer. We compared the preoperative protein profiles with the postoperative (day 14) profiles for the 31 colorectal cancer patients. Two peaks (m/z: 2753.8 and 4172.4, Fig. 2) were detected which were down-regulated in 27 of 31 (87.5%) patients compared to these in preoperative samples. In an independent test set, the two peaks were also validated down-regulated in 13 of 16 (81.3%) postoperative samples.

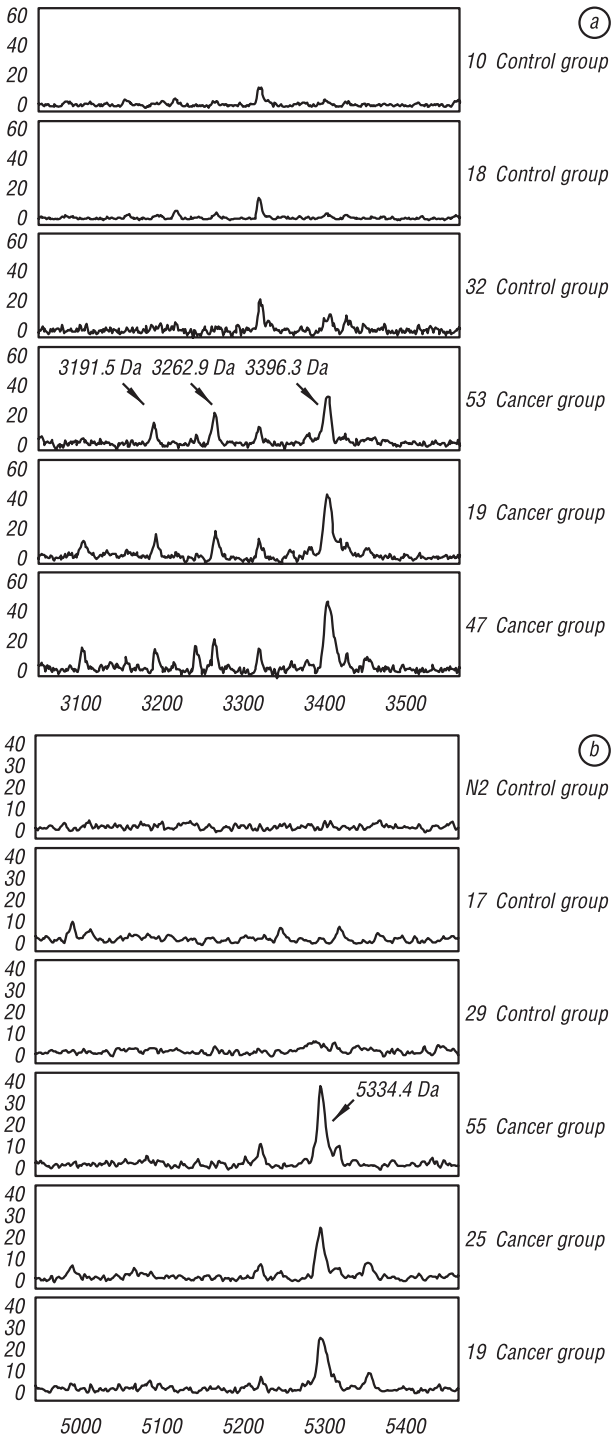

Fig. 1. (*a*, *b*) Proteomic pattern of blood serum samples of colorectal cancer patients and controls evaluated by SELDI-TOF-MS. X-axis represents the ratio of mass to charge of protein, Y-axis represents relative intensity. The profiles demonstrate up-regulation of m/z 3191.5, 3262.9, 3396.3 and 5334.4 peaks in colorectal cancer patients

Differential markers for primary colorectal cancer and metastatic colorectal cancer. The cancer patients of the training set were divided into two groups (30 patients with metastasis and 33 patients without metastasis) according to after surgical examination. Two proteins (m/z: 9184.4 and 9340.9, Fig. 3) were found that can discriminate the two groups. The two proteins were observed in all the Duke'A and in 13 of 15 Duke'B patients, absent in 11 of 14 Duke'C and all Duke'D patients from the test set.

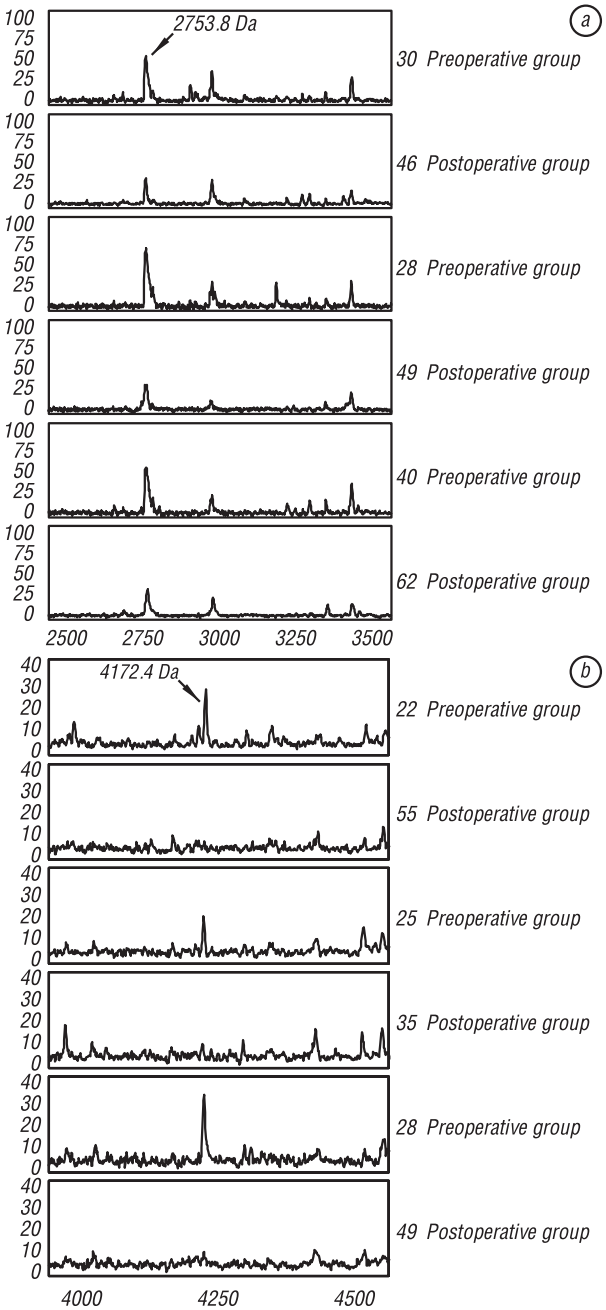

Fig. 2. (*a*, *b*) Proteomic pattern of blood serum samples of preoperative patients and postoperative patients evaluated by SELDI-TOF-MS. X-axis represents the ratio of mass to charge of protein, Y-axis represents relative intensity. The profiles demonstrate up-regulation of m/z 2753.8 and 4172.4 peaks in preoperative patients

DISCUSSION

Although diagnostic technology and therapeutic treatment have made vast progress during the last decades, the survival rate of patients with colorectal cancer still has no significant improvement. Without useful method for early cancer detection is thought to be responsible for this. Currently, CEA is the best available marker for colorectal cancer detection. However, the use of CEA has significant clinical limitation because of low sensitivity (3–66.7%) [4, 12, 13]. Considerable effort has been taken in identifying potential markers that might substitute or complement CEA in screening colorectal cancer.

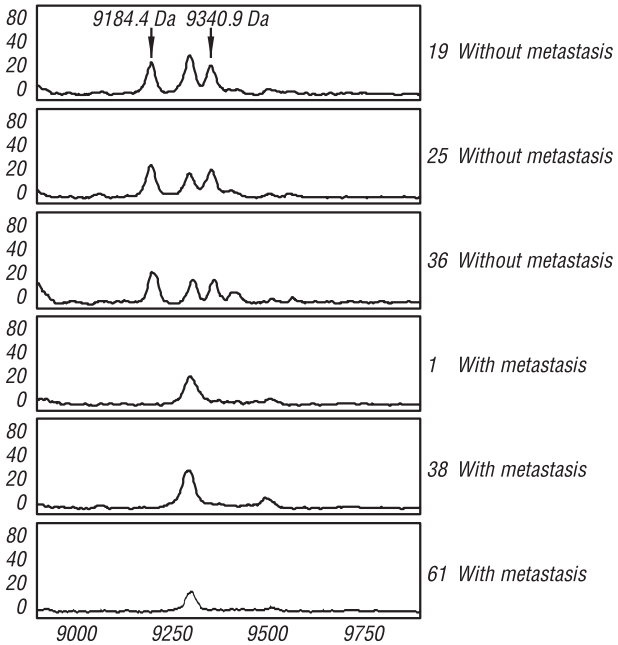

Fig. 3. Proteomic pattern of blood serum samples of colorectal cancer patients with and without metastasis evaluated by SELDI-TOF-MS. X-axis represents the ratio of mass to charge of protein, Y-axis represents relative intensity.The profile demonstrates absence of m/z 9184.4 and 9340.9 peaks in patients with metstatic colorectal cancer

SELDI-TOF-MS is a new type of proteomic platform which has recently shown tremendous promise in the detection of various early-stage cancers, such as breast, ovarian, prostate, gastric cancer and so on [14–17]. It is especially suitable for examination of small volumes of samples such as serum which has been proven to be a rich source of biomarker for the early detection of cancer [18]. Contrary to genome and other conventional approaches, this method can reflect not only the presence of active or inactive genes but also their extent of expression at a specific time point. Furthermore, it can detect all proteins and peptides that may originate from the same gene but with different post-translation modifications. Using SELDI-TOF-MS, novel proteins specific to certain cancer and characterization of these proteins can be discovered and captured by comparative analysis of the mass spectra of the samples from patients and normal controls.

In this study, SELDI-TOF-MS was applied to establish serum protein pattern for screening colorectal cancer. We compared protein spectra from patients who had colorectal cancer with the corresponding spectra from healthy controls and patients with benign colorectal disease. Our analysis yielded a proteomic model consisting of 4 candidate makers (m/z of 3191.5, 3262.9, 3396.3 and 5334.4) which were all up-regulated in cancer patients. Several reports have been made of differential expression of the same m/z values in colorectal cancer, even though different chips were used. In the study [1] it was reported a 3.3×10^3 Da protein to be differentially expressed that was also selected in the final diagnostic pattern. Yu [10, 19] detected a 5.9×10^3 Da protein on a hydrophobic chip which was an up-regulated biomarker in serum of colorectal cancer patients. Although we did not se-

lect the 5904.6 Da protein to form the final diagnostic pattern, it was truly differentially expressed in cancer patients with controls which is consistent with the result [10, 19]. An effective screening test should achieve a high sensitivity and specificity. We were encouraged to find that the proteomic pattern resolved by SELDI may become a potential diagnostic approach with sensitivity of 90.3% and specificity of 95.7% in training set and was validated with high sensitivity and specificity in test set. This study showed that our proteomic biomarkers was significantly better than the combination of routine markers CEA, CA199 and CA242. Eight from ten Duke'A patients from test set were correctly classified by proteomic model but none by the combination of CEA, CA199 and CA242. Thus, these proteomic markers may facilitate early-detection of colorectal cancer.

Finding biomarkers to monitor treatment response is an issue in tumor research. We analyzed proteomic changes in the serum of postoperative patients with colorectal cancer before and after operation. Two peaks (m/z: 2753.8 and 4172.4) were detected which were down-regulated in postoperative samples than preoperative samples. The two proteins were both differential biomarkers between colorectal cancer patients and non-cancer controls and the mean peak intensity were approximately three times in preoperative patients than postoperative patients. We hypothesized that these two biomarker may be oncogene proteins and provide a new insight into therapeutic strategies and molecular mechanism behind the process of tumorigenesis.

Colorectal caner metastasis is a complex process involving multiple changes in gene and protein expression [20–22]. The success of metastatic cancer treatment is strongly dependent on early diagnosis and understanding of the molecule mechanisms and biological behaviors, especially its infiltration and metastasis. To our knowledge, there is no reports about serum proteomics of metastatic colorectal cancer by SELDI-TOF MS before. In this study, the identification of differential proteins between primary colorectal cancer and metastatic cancer was also performed. Two peaks (m/z: 9184.4 and 9340.9) were found that can discriminate the two groups. The two proteins were observed in all the Duke'A and 13 of 15 Duke'B patients and absent in 11 of 14 Duke'C and all Duke'D patients from the test set. We concluded that these two biomarkers may be metastasis related proteins and can be used to monitor micrometastasis at the early stage.

In conclusion, our study has proved that SELDI-TOF-MS is a very useful and promising tool to detect new serum tumor biomarkers. These protein markers will enable a more reliable early diagnosis of colorectal cancer and facilitate the prediction of their progression. To confirm our findings in larger number of study samples and identify the reported biomarker proteins, a prospective study is recently ongoing.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Qingsi He for assistance in tumor samples collection. This work was supported by grants from Science and Technology Special Foundation from Health Department of Shandong Province, China.

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СКРИНИНГ СПЕКТРА БЕЛКОВ СЫВОРОТКИ КРОВИ БОЛЬНЫХ КОЛОРЕКТАЛЬНЫМ РАКОМ МЕТОДОМ SELDI-TOF-MS

Цель: **исследование белкового профиля сыворотки крови больных колоректальным раком и здоровых доноров методом SELDI-TOF-MS для диагностики заболевания и мониторинга микрометастазов.** ***Методы:*** **методом SELDI-TOF-MS исследованы сыворотки крови 63 больных колоректальным раком, 20 больных с доброкачественными новообразованиями прямой кишки и 26 — здоровых доноров. Проведено сравнение профилей белков сыворотки крови 31 больного до и после хирургического вмешательства, а также больных с метастазами или без таковых.** ***Результаты:*** **получена 4-пиковая модель (m/z: 3191,5; 3262,9; 3396,3 и 5334,4), позволяющая отличить опухолевые образцы от неопухолевых с чувствительностью 90,3% и специфичностью 95,7%. Такая модель проверена в тест-системе с чувствительностью 87,5% и специфичностью 93,8%, что является лучшим результатом, чем комбинированное применение CEA, CA199 и CA242 (чувствительность 62,4%) для раннего выявления колоректального рака. Выявлено снижение интенсивности двух пиков (m/z: 2753,8 и 4172,4) при сравнении образцов до и после проведения операции, и идентифицированы два белка (m/z: 9184,4 и 9340,9), позволяющие выявлять больных колоректальным раком с метастазами.** ***Выводы:*** **полученная модель и результаты работы могут быть полезны для диагностики колоректального рака и мониторинга метастазирования.**

Ключевые слова: **SELDI-TOF, протеом, колоректальный рак, биомаркер, метастазирование.**