Biochemical and Biophysical Research Communications xxx (2017) 1–7

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Metabolomic profiling reveals potential biomarkers in esophageal cancer progression using liquid chromatography-mass spectrometry platform

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ARTICLE INFO

Article history:
Received 28 June 2017
Accepted 10 July 2017
Available online xxx

Keywords:
Esophageal squamous cell carcinoma
Metabolomics
Biomarker
Liquid chromatography
Mass spectrometry

ABSTRACT

Esophageal cancer (EC) is one of the most common malignancies with poor prognosis. Metabolomics has been shown to be a powerful approach to discover the potential biomarkers for cancer diagnosis and prognosis. The goal of this study is to screen potential biomarkers for early diagnosis and prognosis. In this study, 40 tissue samples and the corresponding control samples from the same esophageal squamous cell carcinoma (ESCC) patients were analyzed by liquid chromatography-mass spectrometry (LC-MS)-based metabolomics. 20 potential diagnostic biomarkers were selected. Moreover, 9 metabolites were found to be closely correlated with the pathological feature such as local invasion, lymphatic metastasis and postoperative survival time. Glutamate was correlated with local invasion of tumor, and oleic acid, LysoPC(15:0), uracil, inosine and choline were closely related with the lymphatic metastasis, while glutamine, kynurenine, serine and uracil were related with postoperative survival time. The results indicated that the potential biomarkers discovered by metabolomics could reflect the metabolic characterization of ESCC, and offers a novel approach for early diagnosis, assessment and prognosis of the disease.

1. Introduction

Esophageal cancer (EC) is a common malignant tumor of digestive tract. In 2012, an estimated 455,800 new cases of EC were observed worldwide, and 400,200 deaths occurred as a result of EC [1]. Esophageal squamous cell carcinoma (ESCC) is the dominant histological types of EC [2]. Epidemiology of ESCC is characterized by marked differences in prevalence between countries and ethnical groups. The highest incidence and age-adjusted mortality is reached by Kazakh populations, especially in Xinjiang, China [3]. Early diagnosis and treatment of EC is usually with excellent long-term survival (>90%, 5-year survival rate). However, most patients exhibit locally advanced or metastatic EC at the time of diagnosis and have a poor prognosis (<10%, 5-year survival rate) [4]. Clearly, the early diagnosis of EC is very important for improving prognosis of the patients.

Metabolomics, as a growing field in systems biology, involves the global and unbiased definition of the complement of small molecules (<1000Da) in biofluids, tissues, cells, and organs et al. [5]. It has been developed as the significant approach for biomarker discovery, diagnosis, monitoring therapeutic responses and revealing the related pathways in recent years. In general, metabolomics typically employs either nuclear magnetic resonance spectroscopy (NMR) or mass spectrometry (MS), while the latter can be coupled with a separation technique such as gas chromatography (GC), liquid chromatography (LC) or others [6].

Previously, we applied NMR and MS technology to investigate EC metabolic signatures in plasma and urine, finding the

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http://dx.doi.org/10.1016/j.bbrc.2017.07.060
0006-291X/

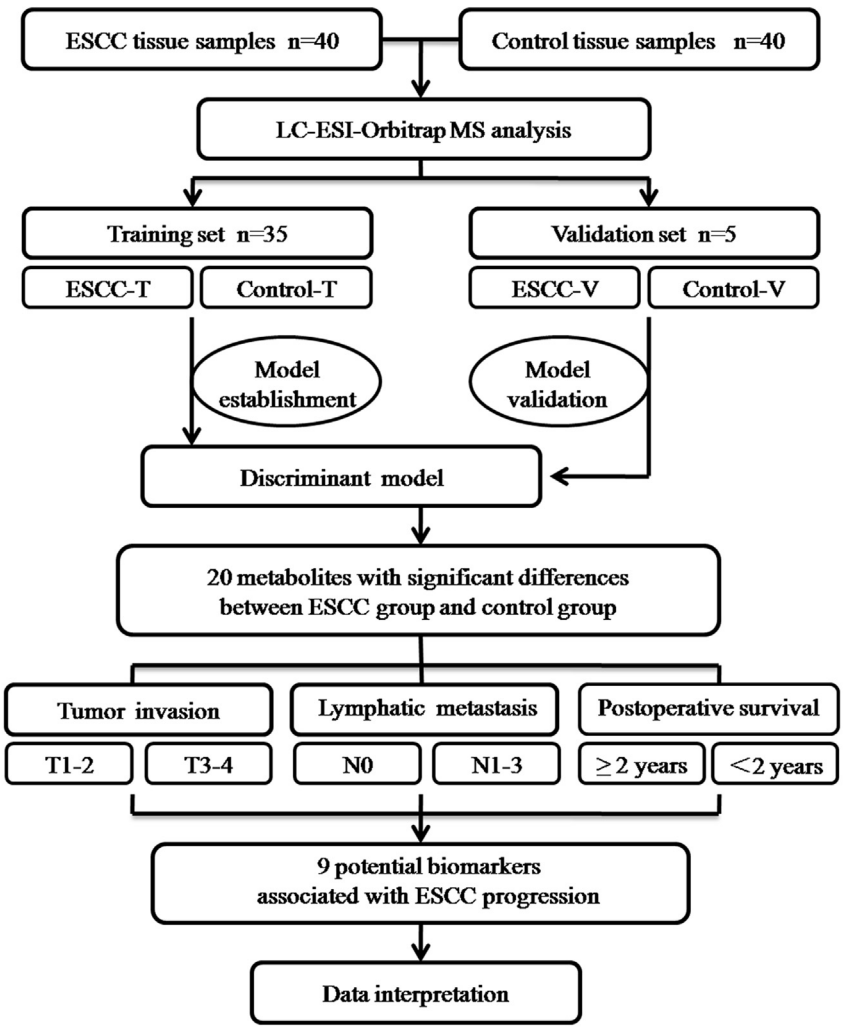
discriminating metabolites for EC and controls which indicating the disturbed metabolism in patients [7,8]. However, it appears that only the extremes can be readily identified from blood or urine samples, and it is possible that the metabolites that have so far been identified may only reflect systemic and therefore advanced disease. From this perspective, tissue samples at or near the site of disease may be more promising. Disappointingly, there are only a few studies focused on the EC tissue samples, and all of them applied GC-MS or NMR platform, which has their own limitations [9–12]. NMR is less sensitive than MS and the major issue of GC-MS is its nature limited to the analysis of small volatile molecules [13].

In this study, ESCC tissue metabolomics was performed by LC-MS. Only the Kazakh population patients were selected. Potential biomarkers were discovered by multivariate data analysis (MVDA). Combined with the pathological feature such as local invasion of tumor, lymphatic metastasis and postoperative survival time, the changes and rules of the metabolites in tissue were analyzed. The results would offer the new approach for early diagnosis, assessment and prognosis of the ESCC. The whole workflow of this study is showed as in Scheme 1.

2. Materials and methods

2.1. Sample collection

40 ESCC patients from the The First Affiliated Hospital of Xinjiang Medical University (Urumqi, China) were enrolled in the study. All subjects gave their informed consent for inclusion before they participated in this study. Cancer stage was established according to the 2009 Tumor Nodes Metastasis (TNM) staging system. All patients were Kazakh race and diagnosed by histopathological examination and accepted surgery. No patients had received chemotherapy or radiation before surgery. The cancer tissues were carefully selected and dissected, corresponding normal tissues were taken at least 5 cm away from tumor. The dissected cancer and normal tissues were firstly snap-frozen in liquid nitrogen and stored at −80 °C before analysis. The patients were treated and followed-up after surgery according to the *Clinical Practice Guidlines for the Diagnosis and Treatment of Esophageal Cancer* developed by Chinese Society of Esophageal Cancer [14]. The detailed demographic profiles of the participants are provided in Table 1.



Scheme 1. Experimental workflow in biomarker discovery. LC-ESI-Orbitrap MS: liquid Chromatography-electrospray ionization -orbitrap mass spectrometry.

Please cite this article in press as: H. Zhang, et al., Metabolomic profiling reveals potential biomarkers in esophageal cancer progression using liquid chromatography-mass spectrometry platform, Biochemical and Biophysical Research Communications (2017), http://dx.doi.org/10.1016/j.bbrc.2017.07.060