Pathology - Research and Practice xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pathology - Research and Practice

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

Identification of clinical tumor stages related mRNAs and miRNAs in cervical squamous cell carcinoma

Chenggang Yang[a,b], Jing Ren[b], Bangling Li[b], Dongmei Zhang[b], Cui Ma[a,b], Cheng Cheng[b], Yaolan Sun[b], Lina Fu[b], Xiaofeng Shi[a,b,*]

[a] Gu'an Bojian Bio-Technology Co., LTD., Langfang, China
[b] Department of BigData, Beijing Medintell Bioinformatic Technology Co., LTD., Beijing, China

ARTICLE INFO

Keywords:
Cervical squamous cell carcinoma
Clinical tumor stage
Differentially expressed mRNAs
Differentially expressed miRNAs

ABSTRACT

Objectives: The aim of this study is to identify the clinical tumor stage related mRNAs and miRNAs, shedding light on the potential molecular mechanisms of cervical squamous cell carcinoma (CSCC).
Methods: Firstly, the mRNA and miRNA next-generation sequencing data were downloaded. Secondly, clinical tumor stage correlation analysis of mRNAs and miRNA was performed, followed by the functional enrichment analysis of all clinical tumor stage related mRNAs. Thirdly, differentially expression analysis of mRNAs and miRNA between different clinical tumor stages was performed, followed by target gene prediction of these differentially expressed miRNAs.
Results: 3 mRNAs (PER1, PRKAB1 and PMM2) and 5 miRNAs (hsa-mir-486, hsa-mir-451, hsa-mir-424, hsa-mir-144 and hsa-mir-450a-2) were overlapped from stage 1, stage 2, stage 3 and stage 4.
Conclusions: Alterations of differentially expressed mRNAs and miRNAs may offer important insights into the molecular mechanisms in the pathology of CSCC.

1. Introduction

Cervical cancer is one of the most widespread tumours of the femalereproductive tract. Cervical squamous cell carcinoma (CSCC) accounts for approximately 90–95% of cervical cancers. It is reported that CSCC is one of the most universal gynecological malignancy that affecting the health of women all over the world [1,2]. CSCC involving the upper genital tract, including the endometrium, ovarian surface and fallopian tubes, that is extremely rare [3–7]. Gungor T et al proposed the possible pathogenic mechanisms of CSCC as follows: (1) *de novo* carcinogenesis; (2) mucosal spread from CSCC; (3) endometrioid adenocarcinoma with predominantly squamous differentiation; (4) extensive squamous metaplasia in the mucosa of the upper genital tract with subsequent malignant transformation [8].

Biewenga P et al found that several pathological factors such as tumor diameter, para metralextension, lymph vascular space invasion, pelvic lymph node metastasis and depth of the stromal invasion were associated with the prognosis of patients [9]. In addition, several novel oncogenes including CISD2, URG4, B3GNT3 and C14ORF166 are associated with the prognosis of the disease [10–12]. Clinically, the standard treatments are chemotherapy, radiotherapy and surgical resection, which are administered based on the clinical tumor stage [13]. However, patients with CSCC still have a high recurrence rate, which has been a serious threat to women's health. Therefore, an understanding of the potential molecular mechanism of the progression of CSCC is a key issue with respect to the treatment of patients with the disease.

In this study, we aimed to find the potential differentially expressed mRNAs and miRNAs in the different clinical tumor stages including stage 1 (well-differentiated), stage 2 (moderately-differentiated), stage 3 (poorly-differentiated) and stage 4 (un-differentiation). We first performed the clinical tumor stage correlation analysis of mRNAs and miRNAs expression data in patients with CSCC through the Cancer Genome Atlas (TCGA) database. Then, functional enrichment analysis of these clinical tumor stage related mRNAs was performed. Next, the screening of differentially expressed mRNAs and miRNAs between different clinical tumor stages was performed followed by the differentially expressed miRNAs-target differentially expressed mRNAs interactions network. Finally, several candidate clinical tumor stage related differentially expressed mRNAs and miRNAs were identified for further understanding the carcinogenesis for CSCC.

* Corresponding author at: Department of BigData, Beijing Medintell Bioinformatic Technology Co., LTD., No. 1, Shanyuan Street, Haidian District, Beijing, 100081, China.
E-mail address: shi.xiaofeng@medintell.com (X. Shi).

https://doi.org/10.1016/j.prp.2018.07.035
Received 9 May 2018; Received in revised form 21 July 2018; Accepted 31 July 2018

Table 1
The clinical information of CSCC.

		Stage I	Stage II	Stage III	Stage IV
Gender	Femal	122	61	42	16
Age	> 50 (Mean ± SD)	62.15152 ± 9.470748	61.37037 ± 8.714039	62 ± 8.428975	61.63636 ± 9.058396
	≤50 (Mean ± SD)	39.52809 ± 7.54997	37.82353 ± 7.30077	41.35 ± 7.249501	41.6 ± 7.861298
Vital status	Alive	100	53	21	5
	Dead	22	8	10	11
Follow-up(days)	> 5 years(Mean ± SD)	8.480235 ± 3.184467	8.172603 ± 2.822871	9.907763 ± 5.79181	11.19452
	< 5 years(Mean ± SD)	1.035644 ± 1.176034	1.208748 ± 1.308062	1.313102 ± 1.470176	1.365845 ± 1.101209
Race	White	86	40	29	7
	Black or African American	14	6	2	3
	Asian	11	1	2	1
	American Indian or Alaska Native	3	4	0	1
	Native Hawaiian or other Pacific Islander	2	0	0	0
	[Unknown]	2	8	6	4
	[Not Evaluated]	3	1	2	0
	[Not Available]	1	1	1	0
Grade	G1	6	5	1	0
	G2	54	25	20	7
	G3	52	22	18	4
	G4	0	1	0	5
	GX	8	6	1	0
	[Not Available]	2	2	2	0

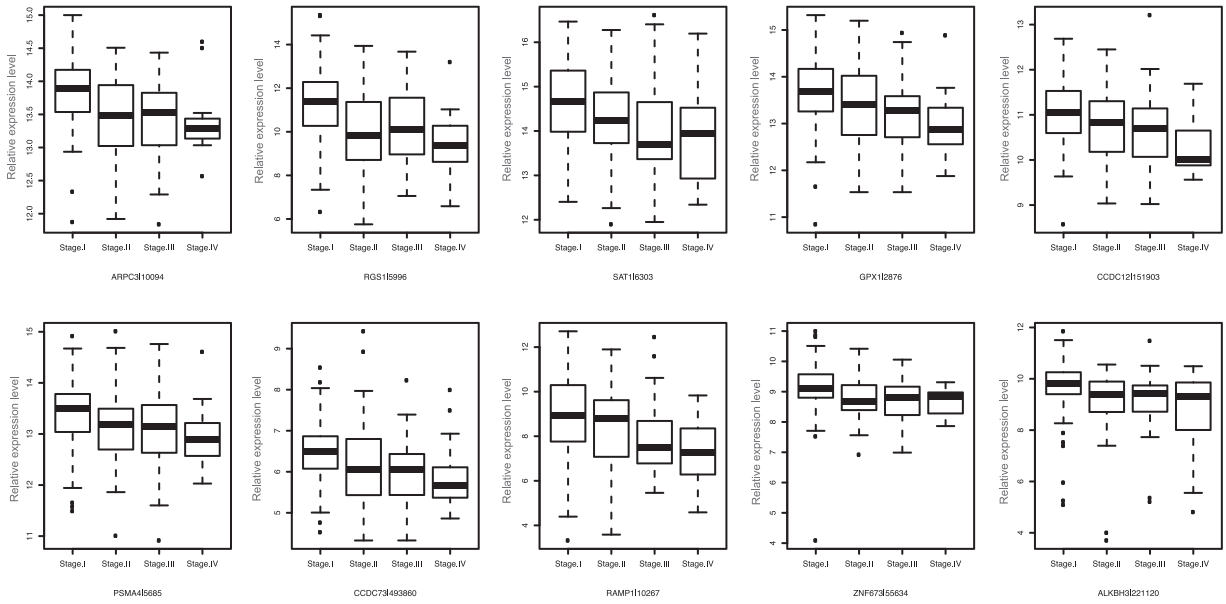

Fig. 1. The box plots of the top 10 clinical tumor stage related mRNAs. The x-axis and y-axis represents the clinical tumor stage and expression quantity, respectively.

2. Materials and methods

2.1. Basic information of patients with CSCC in the TCGA database

A total of 248 CSCC patients with clinical records were available in the TCGA database. Clinical information of these patients was shown in Table 1. The tumor stage of CSCC samples is recorded, which was divided into four stage groups including stage 1 (well-differentiated), stage 2 (moderately-differentiated), stage 3 (poorly-differentiated) and stage 4 (un-differentiated). The inclusion criteria of patients were patients: (1) with a subtype of CSCC; (2) without a history of other malignancy; (3) without a history of neoadjuvant treatment; (4) for whom the expression profiling of mRNA and miRNA was available; and (5) for whom the record of clinical tumor stage was stage 1–stage 4. In the present study, CSCC patients were separated into stage 1, stage 2, stage 3 and stage 4 groups in accordance with the recorded tumor stage. The mRNA sequence data and miRNA sequence data of CSCC patients were downloaded from the TCGA data portal, which is based on UNC IlluminaHiseq_RNASeqV2 and IlluminaHiSeq-miRNASeq, respectively.

2.2. Identification of clinical tumor stage related mRNAs and miRNAs

In this study, those mRNAs/miRNAs with a 0 reads count were excluded. The linear by linear association test [14] was applied to analyze the correlation of the expression of mRNAs and miRNAs with tumor stage by using the lbl.test function of the coin package in R [15]. $P < 0.05$ was considered statistically significant.