Original Article

Comprehensive study of a novel immune-related IncRNA for prognosis and drug treatment of cervical squamous cell carcinoma

Jinhui Liu¹*, Yinghui Liu²*, Feng Gao³*, Jianguo Zhang⁴, Jiadong Pan⁵, Yifei Liu⁴, Hongjun Zhu⁶

¹Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu, China; ²Heilongjiang Institute of Construction Technology, Harbin 150025, Heilongjiang, China; ³Department of Orthopaedics, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu, China; ⁴Department of Pathology, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu, China; ⁵The First School of Clinical Medicine, Nanjing Medical University, Nanjing 211166, China; ⁶Department of Oncology, The Third People’s Hospital of Nantong, Nantong 226001, Jiangsu, China. *Equal contributors.

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Abstract: A comprehensive study focusing on immune-related long non-coding RNAs (IncRNAs) in cervical cancer (CC) was performed. Through the integration of TCGA data, a total of 266 immune-related IncRNAs were obtained. We defined all samples as an entire set, and randomly divided them into train set and test set at a ratio of 1:1. Univariate, LASSO and multivariate Cox regression analyses were carried out based on train set for key IncRNAs (UBL7-AS1, AC083809.1, LIPE-AS1, PCED1B-AS1, ELFN1-AS1 and NCK1-DT) to construct a prognostic model, while the others were used for validation. The overall survival (OS) suggested that we may have longer survival expectancies for patients classified into the low-risk group. The P values of risk score in univariate analysis and multivariate analysis were all less than 0.05, indicating the ability of risk score to independently assess the prognosis of patients. For clinical application, a nomogram with a high degree of agreement between the predicted curve and the actual curve was constructed. Subsequently, immune status and chemotherapy response were investigated in two prognostic subtypes. The associations between risk score and immune cell were estimated, in which CD8+ T cells showed the highest positive correlation and activated mast cell showed the highest negative correlation. In addition, checkpoint proteins (CTLA4, LAG3, PD-1, and TIGIT) showing negative correlation with risk score were found to be upregulated in low-risk group. A total of 3 chemotherapy drugs including paclitaxel, vinorelbine and methotrexate were considered effective in patients of high-risk group. Using 6 key immune-related IncRNAs, we identified two prognostic subtypes and provided new insights for CC immunotherapy.

Keywords: Cervical cancer, prognostic signature, immunity, therapeutic response

Introduction

Among women, cervical cancer (CC) is the fourth common cancer, which accounts for 12160 new cases in United States in 2019 [1]. Presumably, less developed countries are experiencing a higher cervical cancer burden [2]. Recently, the HPV vaccines have been distributed worldwide, which may lead to a decrease in HPV infection and finally a reduced number of cervical cancer cases, however, the severe implication of cervical cancer still cannot be ignored. The research spotlights of therapeutic research for cervical cancer have been developed from DNA vaccines [3-5] to gene silencing in oncoproteins like CRISPR/cas9 systems [6] and gene silencing operated by microRNA [7-9] or regulated by IncRNA [10].

Long noncoding RNA (IncRNA) has become one of the hotspots in cancer research in recent years. RNAs with transcripts ≥200 bp and mostly without protein-coding capacity are defined as IncRNA. Many scholars have reached a consensus on the importance of IncRNAs in organisms, and IncRNAs play a regulatory role in multiple biological processes such as inflammation, immune response, and tumorigenesis. Recently, several oncogenic IncRNAs (IncRNA-CCDST [11], IncRNA-CTS [12], and IncRNA-
NEAT1 [13]) in CC were reported. Meanwhile, immunotherapy has been applied for virally associated cancers including CC [14]. Stevanović et al. reported that metastatic CC associated with papillomavirus showed complete regression after treated by the adoptive T cell. Berger et al. [15] conducted a comprehensive pan-cancer molecular study in CC to identify patients suitable for immunotherapy. However, there was still no comprehensive analysis of immune-related lncRNAs in CC. Hence, we endeavored to search for the molecular mechanisms under immune-related lncRNAs, which may provide new therapeutic strategies for CC.

Material and methods

Data collection

The mRNA expression profiles of cervical cancer (TCGA-CESC) normalized by FPKM and corresponding clinical messages were downloaded from the TCGA database (https://cancergenome.nih.gov). Overall survival (OS), referred to the time from randomization to death due to any cause, was used as the observation endpoint in this study. After clinical information was integrated, 257 samples were defined as an entire set, which was divided into a train set and a test set randomly at a 1:1 ratio. We used the 128-sample train set for calculations, while 129-sample test set and the entire set were used to verify the results of the train set.

Definition of immune-related lncRNA

First of all, two gmt files including “Immune system process M13664” and “Immune response M19817” were downloaded from Molecular Signatures Database v4.0 [16] (http://www.broadinstitute.org/gsea/msigdb/index.jsp). Genes included in these two files were considered as immune-related genes. Second, the list of lncRNAs was determined based on the Ensembl IDs from GENCODE (http://www.gencodegenes.org). Subsequently, corresponding profiles of lncRNAs were separated from mRNA expression data. Finally, based on the results of Pearson correlation analysis using the mRNA expression level of immune genes and lncRNAs, 266 immune-related lncRNAs were screened out with standards of |R|>0.5 and P<0.01.

Construction of a prognostic model

In this paper, a prognostic model was established by the train set, and verified by the test and entire set. The transcript levels of immune-related lncRNAs in the train set were calculated by univariate Cox regression analysis for prognosis-related lncRNAs. The result was subsequently submitted to the LASSO Cox regression and multivariate Cox regression analysis to identify candidate lncRNAs and finally construct a risk linear model. These candidate lncRNAs were attributes with high prognostic values and inapparent correlations. And this model presents patients’ prognostic situation by risk score. Risk score = (β1* expression level of gene 1) + (β2* expression level of gene 2) ... + (βn* expression level of gene n). β was the regression coefficient assessed by the multivariate regression analysis. The tissue samples were divided into high-risk and low-risk groups based on the median risk score.

The prognostic ability of this model was validated by the Kaplan-Meier curve and ROC curve analysis. Principal component analysis (PCA) was employed to observe the expression pattern of two subgroups. Univariate and multivariate analyses were performed to incorporate risk scores and clinical characteristics to demonstrate the independence of the model. These methods have been described previously [17].

Construction of lncRNA-mRNA co-expression network

The potential co-expression relationships between six prognostic lncRNAs and related mRNAs were calculated by Pearson’s correlation analysis (|R|>0.5, P<0.0001). Then, we mapped the lncRNA-mRNA interaction network using Cytoscape visualization software.

Construction and validation of a predictive nomogram

By combining all clinical features (age, stage, grade, and histological type) and risk score, we constructed a nomogram. The nomogram can be used to evaluate the three-year and five-year survival of CC. A calibration plot was used to test the effectiveness of the nomogram, in which predicted probabilities against the actual rates were considered.

Evaluations between immune-related lncRNAs and immune system

The infiltration of 22 types of immune cells in CC was deduced by CIBERSORT [18], a robust
method designed for the estimation of the cell composition of complex tissues based on their gene expression profiles. The fractions of immune cells in CC were assessed. For one thing, the correlations between immune-related lncRNAs and the fraction of immune cells were calculated. For another, the immune infiltration between high-risk and low-risk subgroups was evaluated.

**Gene set enrichment analysis (GSEA) of immune-related lncRNAs**

Gene set enrichment analysis (GSEA) (http://software.broadinstitute.org/gsea/index.jsp) was conducted for the identification of potential functions in six screened lncRNAs. The specific methods for performing GSEA were reported previously [19].

**Chemotherapeutic response prediction**

Since chemotherapy was commonly used to treat CC, the chemotherapeutic response of each patient, which was determined by the half-maximal inhibitory concentration (IC$_{50}$), was estimated by R package “pRRophetic” based on the Genomics of Drug Sensitivity in Cancer (GDSC) (https://www.cancerrxgene.org/) [20].

**Statistical analysis**

All statistical analyses were conducted by R version 4.0.5 environment (R package: ggplot2, glmnet, forest plot, rms, survminer, survival ROC, heatmap, pRRophetic). Two-tailed $P \leq 0.05$ was regarded as statistical significance if not noted otherwise.

**Results**

**Definition of immune-related lncRNAs**

Based on two gmt files (“Immune system process M13664” and “Immune response M19817”) from Molecular Signatures Database v4.0, 331 immune-related genes were determined. Based on the results of Pearson coefficient between immune genes and lncRNAs, a total of 266 lncRNAs with standards of $|R|>0.5$ and $P<0.0001$ were defined as immune-related lncRNAs.

**Construction of a six-lncRNA immune-related model for CC patients**

In recent years, people have been trying to construct prognosis models based on univariate Cox regression analysis and LASSO Cox regression. However, the results were random and require independent verification. To make the calculated results more universal, the entire set (n=257) was randomly divided into a train set and a test set at a 1:1 ratio. Subsequently, univariate Cox regression analysis (Supplementary Table 1), LASSO Cox regression (Figure 1A, 1B) and multivariate Cox regression analysis (Figure 1C) were performed based on the train set, from which six key lncRNAs (UBL7-AS1, AC083809.1, LIPE-AS1, PCED1B-AS1, ELFN1-AS1, and NCK1-DT (also known as NCK1-AS1)) were screened out. In GEPIA, UBL7-AS1, LIPE-AS1, PCED1B-AS1 and NCK1-DT were upregulated in tumors (Supplementary Figure 1A). In addition, the Kaplan-Meier survival analysis base on GEPIA showed that UBL7-AS1, LIPE-AS1, and PCED1B-AS1 were associated with patients’ survival, but NCK1-DT was not (Supplementary Figure 1B). Immune-related genes that showed high correlations with six key lncRNAs were plotted by Cytoscape (Supplementary Figure 2).

The risk score of an individual patient = (-0.516* expression value of UBL7-AS1) + (0.16645* expression value of AC083809.1) + (-0.5085* expression value of LIPE-AS1) + (-0.3332* expression value of PCED1B-AS1) + (0.09857* expression value of ELFN1-AS1) + (-0.1387* expression value of NCK1-DT).

The risk score in train group ranges from 0.0084 to 73.4069.

**Evaluations of the prognostic model**

The risk score for all CC patients was calculated according to the formula mentioned above and ranked in ascending order. The median risk score for the train set was 1.0296. Patients were divided into low-risk and high-risk groups based on this value (Figure 2A). Patients’ survival status in each subgroup was displayed by dot plot (Figure 2D), from which we can conclude that the survival status of patients in the low-risk group is better than that in the high-risk group. The Kaplan-Meier survival analysis also indicated that the OS of patients in low-risk subgroup was prolonged compared with that in the high-risk subgroup (Figure 2G). The stratified analysis showed that two prognostic subtypes can be distinguished in patients with Age ≤50, with squamous histological type, stage I & II, and grade 3 & 4 (Supplementary Table 2)
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Figure 3. The ROC curves based on the train set showed that this model could predict patients’ 1-year survival with AUC value at 0.775, 3-year at 0.748, and 5-year at 0.746 (Figure 2J). Besides, there was a clear separation between low-risk and high-risk subgroups when principal components analysis was performed based on six key IncRNAs (Figure 2M). The verification was then conducted on the test set (Figure 2B, 2E, 2H, 2K, 2N) and the entire set (Figure 2C, 2F, 2I, 2L, 2O). In Kaplan-Meier survival analysis, this model separated patients with different prognosis. In the ROC curve, this model also showed high accuracy. In PCA, the results also suggested heterogeneity between high- and low-risk subgroups. These results guarantee the credibility and practicality of our data.

To explore whether risk score is an independent predictor for patient prognosis, the univariate analysis and multivariate analysis incorporating clinical factors were conducted. The results based on the train (Figure 3A), test (Figure 3B), and entire set (Figure 3C) all revealed that risk score could be independent of other clinical factors and effectively predict the prognosis of patients (P<0.05). Meanwhile, the multi-factors ROC (Figure 4A, 4B) curve was performed integrating clinical factors.
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Figure 2. An overview of the prognostic model. Rank of risk score and distribution of train set (A), test set (B) and entire set (C). CC samples were divided into low- and high-risk subgroups based on the median value of the risk score calculated in train set (D). Samples in test set (E) and entire set (F) were also divided based on the median value calculated in train set. The survival status and survival time of patients with CC ranked by risk score. (A-F) Green dots represent patients with a low level of risk score and red dots represent patients with a high level of risk score. The Kaplan-Meier survival analysis based on the median value of the risk score in train set (G), test set (H) and entire set (I). The ROC analysis of risk score in 1-, 3-, and 5-year survival in train set (J), test set (K) and entire set (L). Principal components analysis (PCA) showed different distributions in high- and low-risk group, suggesting a distinct transcript composition in two prognostic subtypes in train set (M), test set (N) and entire set (O).
Comparing with clinical factors, risk score showed higher prediction accuracy in 3 years (AUC=0.722) and 5 years (AUC=0.727). A nomogram (Figure 4C) containing risk score and clinical factors was constructed. The C-index of this nomogram was 0.67, which indicated acceptable predictive ability. What’s more, the predicted survival was close to the actual survival situation in the 3-year (Figure 4D) and 5-year (Figure 4E) calibration curve. Taking together, these results indicated that this nomogram shows good performance in predicting the OS of CC patients.

**Gene set enrichment analyses**

According to the median risk score, patients were divided into high-risk and low-risk groups, and GSEA (Figure 5) was performed between...
two groups to explore possible pathway explanations in CESE. And GSEA (Figure 5) was performed to explore potential pathways account in CESE. Representative KEGG pathways in low-risk group were “B cell receptor signaling pathway”, “chemokine signaling pathway”, “intestinal immune network for IgA production”, “natural killer cell mediated cytotoxicity”, “primary immunodeficiency”, “T cell receptor signaling pathway”, and “Toll-like receptor signal-
ing pathway”. Immune-related pathways were enriched in the low-risk group. Meanwhile, representative KEGG pathways in the high-risk group were “ECM receptor interaction” and “focal adhesion”, which were frequently dysregulated pathways in cancer [21, 22].

**Exploration of immune status and chemotherapeutic response in high- and low-risk subgroups**

We developed a robust prognostic model based on the immune-related lncRNAs. Based on this model, we tried to explore the main immune cells that function in tumors. Using CIBERSORT, the infiltration fractions of immune cells in CC were first estimated. Spearman’s rank correlation coefficients between risk score and immune infiltration in CC (Figure 6A) were calculated, in which CD8+ T cells showed the most positive correlation (Figure 6B) and activated mast cell showed the most negative correlation (Figure 6C). Other figures revealing the association between risk score and immune cells were shown in Supplementary Figure 4. Meanwhile, we compared the infiltration fractions of immune cells in the high-risk and low-risk groups. Dendritic cells, macrophages, T cells and mast cells demonstrated significant differences between high- and low-risk groups (Figure 6D). Among which, gamma delta T cells, CD8+ T cells, Tregs, resting dendritic cells, and resting mast cells revealed higher fraction in low-risk patients; while activated dendritic cells, activated mast cells, CD4+ memory resting T cells and M0 macrophages account for a higher proportion of high-risk patients. Subsequently, the Pearson correlation coefficient was calculated between six key lncRNAs and the infiltration fractions of 22 types of immune cells (Figure 6E). NCK1-DT showed frequent contact with immune cells, suggesting an important role that this lncRNA played in biological progress.

Immune checkpoint proteins were reported to function in immune response, and 7 molecules (including CTLA4, IDO1, LAG3, PD-1, PD-L1, PD-L2, and TIGIT) played the main role in biological progress [23]. The Spearman’s rank correlation coefficients showed negative correlations between immune checkpoint modulators and risk score (Figure 7A). CTLA4, LAG3, PD-1, and TIGIT were found to be upregulated in the low-risk patients (Figure 7B).

Cisplatin and paclitaxel are the first-line chemotherapy for CC. Hence, we tried to investigate the chemotherapeutic responses between high-risk and low-risk patients to provide patients with more appropriate treatment strategies. High-risk patients showed increased sensitivity to three of ten conventional chemotherapeutic drugs (paclitaxel, vinorelbine and methotrexate) (Figure 8). These results can be helpful for the precise treatment of CC.
Discussion

Over the past decades, the exploration of cancer therapy mainly focused on two distinct ways. For one thing, efforts were taken to understand the underlying genetic drivers of tumorigenesis, which promotes the development of clinically important targeted drugs. For another, the attempt to activate or guide the protective tumor immunity to correctly identify tumor cells in the human body also provides new therapeutic strategies, for example, using the immune checkpoint antibodies to reverse the negative regulators of T cell function. Hence, we endeavored to search for new therapeutic strategies for CC based on “genetic code” and “immunity”.

Meanwhile, with the increasing development of high-throughput sequencing, various non-cod-
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Figure 7. Seven immune checkpoint immunomodulators and risk score. A. The Spearman’s rank correlation coefficients between 7 immune checkpoint modulators (CTLA4, IDO1, LAG3, PD-1, PD-L1, PD-L2, and TIGIT) and risk score. B. CTLA4, LAG3, PD-1, and TIGIT were found to be upregulated in low-risk group (P<0.05).
Figure 8. The chemotherapeutic responses of two prognostic subtypes to ten conventional chemotherapy drugs. Three chemotherapy drugs including paclitaxel, vinorelbine and methotrexate were considered effective in patients of high-risk group.
ing RNAs like IncRNA and circRNA [24] were found to enroll in the biological pathways. Heretofore, certain miRNAs and mRNAs showing tumor specificity in CC have been reported. However, there was still no bioinformatics researches in CC based on immune-related IncRNAs.

In this paper, we tried to identify the pathogenic mechanisms of CC from immune-related IncRNAs. And a prognostic model integrating six immune-related IncRNAs (UBL7-AS1, AC083809.1, LIPE-AS1, PCED1B-AS1, ELFN1-AS1, and NCK1-DT) was deemed as a prognostic reference factor for CC. The expression of six immune-related IncRNAs could be converted by this model through a specific formula to present the prognosis of CC patients, which was quantified by risk score. Based on this innate characteristic, each patient could be discriminated with a favorable or poor prognosis (Figure 2). Patient with high-risk score means unfavorable result. The PCA suggested that our prognosis model was effective in distinguishing the high-risk group from the low-risk group. Besides, mostly immune checkpoint proteins were upregulated in the low-risk group (Figure 7B). Therefore, this grouping method may help patients choose whether to carry out immunotherapy in the future. The univariate analysis and multivariate analysis indicated that risk score was an independent factor to forecast the overall survival. The forest plot of HR value (HR>1) also informed that the risk score is representative of a harmful factor (Figure 3). What’s more, compared with conventional clinical factors, this prognostic model showed higher prediction accuracy.

This prognostic model was constructed following the expression of six IncRNAs, among which, UBL7-AS1, LIPE-AS1, PCED1B-AS1, and NCK1-DT were upregulated in tumors (Supplementary Figure 1A). In addition, UBL7-AS1, LIPE-AS1, and PCED1B-AS1 were associated with patients’ survival. We searched for previous research foundations of these IncRNAs. The joining of UBL7-AS1 to RUNX1 happens in patients with myelodysplasia [25]. The IncRNA LIPE-AS1 was downregulated after exposure to DNA damage in lung and liver cancer cells [26]. PCED1B-AS1 was mainly reported to be associated with glioma [27, 28]. Surprisingly, a study reported that upregulated PCED1B-AS1 could lead to apoptosis and autophagy of macrophages in active tuberculosis [29]. In our analysis (Figure 6B), there was a negative correlation between PCED1B-AS1 and M1 macrophages (Compared with M2 macrophages, it has a higher tumor-suppressing effect). Does PCED1B-AS1 also play a role in CC through M1 macrophages? This may be an idea worth studying. ELFN1-AS1 was associated with the proliferation and migration of colon adenocarcinoma [30-32]. NCK1-DT has the most complex relationship with immune cell infiltrations in our study (Figure 6B). It is currently reported that the up-regulated NCK1-DT can promote tumor development through the mechanism of ceRNA [33-35]. What’s more, high levels of NCK1-DT can lower the sensitivity of cervical cancer cells to cisplatin chemotherapy [36]. However, there was no report of AC083809.1. Most of these IncRNAs were upregulated in tumors, which suggested that the high expression of these IncRNAs may have caused the imbalance of the intracellular environment.

We also paid attention to the correlation between infiltrating immune cells and IncRNAs in CC. NCK1-DT was the most active IncRNA in the prognostic model, showing the most positive correlation with CD8+ T cells and negative correlation with mast cells in CC. The fraction of CD8+ T cells was upregulated in the low-risk group, which indicated the protective effect of this cell. Human papillomaviruses (HPVs) are the primary etiologic agents of cervical cancer, which progress with persistent expression of the oncoproteins E6 and E7. Çuburu et al. [37] designed an adenovirus vector-based prime-boost vaccination to induce cervicovaginal CD8+ T cell responses against corresponding oncoproteins. Meanwhile, the role of mast cell functions in cancer is still controversial. In our analysis, activated mast cells occupied a higher proportion in the high-risk group, and resting mast cells showed the opposite result. Therefore, it is worth talking about the role of mast cells in CC.

Finally, we endeavored to estimate the chemotherapeutic response of each patient based on IC50. A total of 3 chemotherapy drugs including paclitaxel, vinorelbine, and methotrexate were considered effective for patients in the high-risk group.

Limitations can be seen in our research and our results should be treated with caution.
First, although we performed in-group verifications in the test and entire groups, an independent database for external validation is required. Second, the efficiency of the prognostic model and conjecture based on results has yet to be resolved.

Conclusion

A prognostic model with robust forecasting ability for CC patients was constructed based on six immune-related lncRNAs. This may provide a new treatment strategy for the immunological treatment of CC.

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Disclosure of conflict of interest

None.

Abbreviations

CC, cervical cancer; OS, overall survival; PCA, principal component analysis; GSEA, gene set enrichment analysis; GDSC, the Genomics of Drug Sensitivity in Cancer; IC50, the half maximal inhibitory concentration; LASSO, the least absolute shrinkage and selection operator; HPV16, human papillomavirus.

Address correspondence to: Dr. Hongjun Zhu, Department of Oncology, The Third People's Hospital of Nantong, No. 99 Qingnian Middle Road, Nantong 226001, Jiangsu, China. Tel: +86-513-85051875; E-mail: zhj28254282@163.com; Dr. Yifei Liu, Department of Pathology, Affiliated Hospital of Nantong University, No. 20 Xisi Road, Nantong 226001, Jiangsu, China. Tel: +86-513-85051875; E-mail: ntdxiuyifei@sina.com

References

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### Supplementary Table 1. The result of univariate Cox regression analysis

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Supplementary Figure 1. An overview of six immune-related lncRNAs in CC. The expression (A) and corresponding significant OS analysis (B) of UBL7-AS1, LIPE-AS1, PCED1B-AS1 and NCK1-DT downloaded from GEPIA.
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Supplementary Figure 2. The mRNA-lncRNA co-expression networks based on six immune-related lncRNAs.

Supplementary Figure 3. Two prognostic types could be distinguished in patients with age ≤50, squamous histological type, stage I & II, and grade 3 & 4.
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Supplementary Figure 4. The Spearman’s rank correlation coefficients between risk score and immune cells (activated dendritic cells, eosinophils, M0 macrophages, resting mast cells, activated NK cells, activated memory CD4+ T cells, resting memory CD4+ T cells and Tregs) in CC.