A novel endoplasmic reticulum stress-related lncRNA prognostic risk model for skin cutaneous melanoma

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Research Article

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Abstract

Objective

Endoplasmic reticulum stress(ERS) and Long non-coding RNAs (lncRNAs) play a important role in the occurrence and progression of melanoma. This study aimed to explore the prognostic impact of ERS-associated lncRNA profiles on cutaneous cutaneous melanoma (SKCM).

Methods

Get the raw date of SKCM from The Cancer Genome Atlas(TCGA). The ERS-related genes were obtained from the GSEA website, and then the ERS-related LncRNAs were obtained through the mRNA and LncRNA co-expression network. A prognostic risk model for the composition of ERS-related lncRNAs was identified by lasso regression analysis. Divided patients into high-risk and low-risk groups based on the model's risk score. Differences in survival outcomes, immune infiltration, chemotherapeutic drug sensitivity, and immune checkpoint gene expression were then assessed between the two groups.

Results

Thirty-nine ERS-related lncRNAs associated with prognosis were obtained. A prognostic risk model consisting of 10 ERS-related lncRNAs was identified. Patients in the low-risk group had a better prognosis than those in the high-risk group. Analysis of the tumor microenvironment revealed that risk scores correlated with infiltration of immune cells in 8. Patients in the low-risk group were more sensitive to the chemotherapy drugs paclitaxel and cisplatin than in the high-risk group.

Conclusion

This study identified a risk model composed of 10 ERS-related lncRNAs with significant prognostic value in SKCM and could provide guidance for clinical treatment.

Introduction

Skin cutaneous melanoma(SKCM) was a tumor characterized by the abnormal proliferation of epidermal melanocytes, which are susceptible to genetic mutation by changes in external factors[1,2]. Currently, the global incidence of SKCM is increasing at a faster rate each year than other tumors. According to global cancer statistics[3], there were an estimated 290,000 new cases of melanoma and approximately 60,000 death in 2008. Melanoma was a highly malignant skin cancer with a poor prognosis and easy to metastasize[4]. Therefore, it is very necessary to find new melanoma prognostic markers, which can better guide clinical treatment.

The endoplasmic reticulum (ER) provides the site for protein folding, transport, and maintenance of cellular function. Endoplasmic reticulum stress(ERS) occurs when cellular homeostasis collapses. In malignant cells, proliferation was rapid and increased synthesis of the desired mutant form of the protein induces the accumulation of misfolded proteins, so tumor cells often experience ERS[5]. Tumor cells adapt to it to survive and may suffer from apoptosis if they do not handle ERS well. A study have shown that both ERS and autophagy are involved in melanoma progression and chemotherapy resistance[6]. Chen et al identified six autophagy-related lncRNAs associated with melanoma prognosis by bioinformatics analysis[7]. ERS can induce the production of autophagy, so it is possible to search for one or more ERS-related signature genes to predict the prognosis of SKCM.

Although long non-coding RNAs (lncRNAs) cannot perform DNA transcription and translation, they can exert biological functions by interacting with DNA or proteins to regulate protein expression levels[8]. As one of cancer biomarkers, lncRNAs were involved in the epigenetic, transcriptional and post-transcriptional regulation of various cancers and thus affect the occurrence and development of cancers[9–11]. Recently, more and more studies have shown that lncRNAs can serve as prognostic biomarkers in melanoma, including autophagy-related lncRNAs[7], immune-related lncRNAs[4] and tumor microenvironment-related lncRNAs[12]. However, no studies have reported the impact of ERS-related lncRNAs on the prognosis of SKCM.

In this study, we screened 39 ERS-related lncRNAs associated with SKCM prognosis by analyzing the expression dataset from SKCM in the TCGA database. Finally, we identified a risk model consisting of 10 ERS-associated lncRNAs with the potential to predict survival outcomes in SKCM patients.

Methods And Material

Raw data acquisition

Transcriptome RNA-seq data and corresponding clinical data for 471 skin cutaneous melanoma(SKCM) samples were downloaded from the TCGA database. Among them, 321 patients with complete follow-up data and complete clinicopathological data were included in the follow-up analysis. The clinical information of the patients is shown in Table 1.

Identification of ERS-related lncRNAs in SKCM

1613 endoplasmic reticulum stress(ERS)-related genes(GSEA:M845) were obtained from Molecular Signatures Database of Gene Set Enrichment Analysis (GSEA -(https:/ /www.gsea-msigdb.org/gsea/index.jsp)). And 14142 ERS-related lncRNAs were identified by constructing ERS-related mRNA-lncRNA co-expression network according to the criteria of |Correlation Coefficient| > 0.4 and P < 0.001.

Consensus cluster analysis□tumor microenvironment and immune cell infiltration analysis

ERS-related lncRNAs associated with SKCM prognosis were selected for further analysis. Then, cluster analysis of SKCM was performed using the "ConsensusClusterPlus" package to classify into different subtypes. Gene expression patterns between each subtype were assessed and visualized by the "pheatmap" package. Meanwhile, we examined the function of each SKCM subtype by gene set enrichment analysis (GSEA) with a simulation of 1000 and an FDR of 0.05.

Scored using the 'estimation' package, calculating the immune score, stromal score, and estimated score for each SKCM patient. The levels and proportions of infiltration of 22 immune cell types in each SKCM sample were analyzed using CIBERSORT. Furthermore, we assessed differences in different immune cell fractions between different clusters.

Construction of risk score formula

ERS-related lncRNAs associated with survival were identified by univariate cox regression analysis. ERS-associated lncRNAs with p-values <0.001 were then further incorporated into LASSO regression analysis to develop lncRNA signatures and construct a prognostic risk model using the "glmnet" package in R software. And the "caret" package was used to split the SKCM samples into training and testing groups. The formula is as follows: risk score = $\sum$RNAi × $EXP_{lncRNAi}$.(RNAi :regression coefficient; EXP_{lncRNA} : lncRNA expression level). Patients in the training and testing cohorts were divided into high-risk and low-risk groups based on median risk scores. The correlation between risk score and immune cell abundance was visualized using 'ggplot2'. In addition, the differences in the expression of different immune checkpoint genes in the high-risk and low-risk groups and the differences in the sensitivity of the two groups to different chemotherapy drugs were also calculated.

Assessment of ERS-lncRNA signature

Survival probabilities between high-risk and low-risk groups of SKCM patients were estimated using the survival and survminer R packages. ROC analysis was used to assess the sensitivity and specificity of lncRNA signatures. All analyses were performed in the train and test groups.

Validation of the ERS-related lncRNA signature

Univariate and multivariate Cox regression analyses were performed in the training and test groups, respectively, and confirmed that the risk model constituted by ERS-related lncRNAs could serve as a risk factor for independent prognosis of SKCM. The predictive accuracy of the prognostic risk model was also assessed using the area under the curve (AUC).

Statistical analysis

The tool for data analysis was R software (version 4.1.2). Principal component analysis (PCA) for efficient dimensionality reduction, pattern recognition, and exploratory visualization of high-dimensional data from genome-wide, risk models of 1613 ERS-related coding genes and 10 ERS-related lncRNA expression profiles. The criterion to be considered statistically significant was $P < 0.05$.

Results

Identification of ERS-related lncRNAs

By constructing the co-expression network of mRNA and lncRNA, a total of 14,142 ERS-related lncRNAs were obtained. Then, 39 ERS-related lncRNAs were found to be associated with survival prognosis in skcm patients using univariate Cox regression analysis ($P < 0.001$) (Figure.1A). We analyzed the differential expression of 39 ERS-related lncRNAs in normal tissues and SKCM (Figure. 1B), and analyzed the correlation between these lncRNAs and PD-L1 (Figure. 1C).

Consensus clustering of SKCM patients based on ERS-related prognostic lncRNAs

Based on the differential expression of ERS-related prognostic lncRNAs in different SKCM patients, patients were divided into different subgroups using consensus clustering. Based on the similarities shown by ERS-related prognostic lncRNA expression levels, we found that each cluster had the highest stability when k = 2 (Figure. 2A). SKCM patients were divided into cluster 1 of 168 patients and cluster 2 of 290 patients (Fig. 3(a)). Compared with skcm patients in cluster 2, patients in cluster 1 had a higher overall survival rate (Figure. 2B, $p \leq 0.001$). Interestingly, we also found some correlation between patients in cluster 2 and advanced clinical stage (Figure. 2C).

Consensus Clustering related to tumor microenvironment

By immune scoring patients in cluster 1 and cluster 2, we found differences between the two clusters in the level of immune cell infiltration, which gave us a better understanding of the role of ERS-related prognostic lncRNAs in the immune microenvironment of SKCM. The scores in cluster 1 were higher than those in cluster 2, whether it wass immune score, matrix score, or estimated score (Figure 3A-C). Figure 3D presents the infiltration abundance of 22 types of immune cells in cluster 1 and cluster 2. We found significant differences in the degree of infiltration of 12 immune cells in cluster 1 and cluster 2, which were B cells memory, Plasma cells, T cells CD8, T cells CD4 memory activated, T cells follicular helper, T cells regulatory, NK cells resting, Macrophages M0, Macrophages M1, Macrophages M2, Dendritic cells resting and Mast cells activated(supplement figure1).

Enrichment analysis of 2 SKCM subtypes

We explored the underlying regulatory mechanisms responsible for the differences between the two clusters of SKCM patients by performing KEGG enrichment analysis in GSEA. The top five pathway enrichments significantly associated with cluster 1 and cluster 2 are showed in Figure 5. Chemokines, cytokine receptor interactions, and JAK-STAT signaling pathways were found to be associated with cluster 1, While cluster 2 is mainly associated with RNA polymerase and aminoacyl tRNA biosynthesis.

Construction of a ERS-related prognostic lncRNA signature

The 39 prognostic ERS-related lncRNAs obtained were further analyzed by lasso regression, and a prognostic diagnostic risk model consisting of 10 ERS-related lncRNAs(AATBC, ZEB1-AS1, LINC01871, AC093726.1, AC021188.1, AC092747.4, AC009495.2, AL157871.2, AC242842.1 and AC067930.4) was obtained. The coefficient and partial likelihood deviance of prognostic signature are presented in Figures 6A and Figures 6B. By random assignment, 230 SKCM patients were assigned to the training cohort and 228 SKCM patients were assigned to the testing cohort. The 10 ERS-related lncRNAs and their corresponding risk coefficient are showed in table2. Risk score for each patient: Risk score = [(0.051* Exp (AATBC) + (-0.276* Exp (ZEB1-AS1) + (-0.118* Exp (LINC01871) + (-0.004* Exp (AC093726.1) + (-0.101* Exp (AC021188.1) + (-0.017* Exp(AC092747.4) + (0.142* Exp(AC009495.2) + (-0.045* Exp(AL157871.2) + (-0.067* Exp(AC242842.1)+ (-0.127* Exp(AC067930.4)]. Then, according to the risk score, SKCM patients were divided into high-risk and low risk groups. Figure 7 shows the distribution of survival probability(Figure 7A and Figure 7E), survival time(Figure 7C and Figure 7G), risk score((Figure 7B and Figure 7F) and lncRNA signature ((Figure 7D and Figure 7H)) of each SKCM patient in the training and testing cohort. In both the training cohort and the test cohort, the prognosis was better in the low-risk group than in the high-risk group, both in terms of survival probability and survival time(Figure7A).

Univariate regression analysis showed that T stage, N stage, clinical stage and risk score were associated with survival prognosis in both training cohort and testing cohort(Figure 8B and Figure 8E). Further analysis by multivariate regression showed that T stage, N stage and risk score were still significantly associated with prognosis(Figure 8C and Figure 8F). Therefore, we believed that the risk score can serve as an independent prognostic risk factor for patients with SKCM. The ROC curve analysis showed that the risk score had a high predictive accuracy for patient prognosis in both training cohort and testing cohort, with areas under curve(AUC) of 0.709(Figure 8A) and 0.719(Figure 8B), respectively.

In addition, we validated the prognosis of risk scores in different groups of SKCM patients and found that in both male (Supplementary Figure. 2C) and female (Supplementary Figure. 2D), and SKCM patients older than 65 years or younger (Supplementary Figure. 2A-B) , the high-risk group had a worse prognosis.

Furthermore, among SKCM patients with advanced clinical stage (Supplementary Figure. 3A), pT3-4 (Supplementary Figure. 3B), pM0 (Supplementary Figure. 3C), and pN1-3 stage (Supplementary Figure. 3D), the low-risk group had a better prognosis compared with the high-risk group,.

Correlations between risk scores and clinical characteristics

AATBC and AC009495.2 were highly expressed in the high-risk group, and the remaining 8 lncRNA signature(ZEB1-AS1, LINC01871, AC093726.1, AC021188.1, AC092747.4, AL157871.2, AC242842.1 and AC067930.4) were mainly highly expressed in the low-risk group(Figure 8A). The heatmap in Figure 8 also showed the differential expression of patients in 2 different risk groups in terms of pN stage, clinical stage, immune score, and cluster subtype. The risk score increased when pT stage increased. In addition, groups with higher immuneScore had higher risk scores compared to group with lower immuneScore.

Risk Score Associated with Immune Infiltration

Risk scores were negatively correlated with the infiltrating abundance of B cells memory, Macrophages M1, T cells CD4 memory activated, T cells CD8 and T cells follicular helper(Figure 9A-E). But the risk score was positively correlated with the infiltrating abundance of immune cells such as Macrophages M0, Macrophages M2 and Mast cells resting(Figure 9F-H).

Response of high-risk and low-risk patients to chemotherapy, targeted therapy, and Immunotherapy

The pRRophetic algorithm was used to predict the IC50 of three common chemotherapeutic agents (docetaxel,cisplatin and paclitaxel) and one common targeted therapeutic agents in high-risk and low-risk patients. There were significant differences in the sensitivity to cisplatin, paclitaxel, and sorafenib between patients in the high-risk group and the low-risk group (Figure 9I-K). Figure 9I-K reveals that patients in the low-risk group are more sensitive to the chemotherapy drugs paclitaxel and cisplatin than those in the high-risk group. However, patients in the high-risk group were more sensitive to sorafenib than those in the low-risk group (Figure 9K). To investigate the potential susceptibility of SKCM patients to immune checkpoint (PD-L1, CTLA-4, HAVCR2, LAG-3, PDCD1, or VSIR) inhibitors, we compared the differences in immune checkpoint gene expression between high-risk and low-risk patients. The results showed that the expression levels of these six immune checkpoint genes in the low-risk group were higher than those in the high-risk group (Figure 9 L-Q). These data suggest that low-risk patients may respond better to immune checkpoint inhibitors targeting PD-L1, CTLA-4, HAVCR2, LAG-3, PDCD1 or VSIR than patients in the high-risk group.

Different ERS statuses in low-risk and high-risk groups

By performing principal component analysis (PCA) on risk models of 10 ERS-related lncRNAs, 1613 ERS-related coding genes and genome-wide expression profiles from TCGA (Supplementary Fig. 4), we found that low-risk and high-risk groups were distributed in two different direction (Supplementary Figure 4). It showed that the risk model could divide SKCM patients into two parts, and the ERS status of SKCM patients differed in high-risk and low-risk groups.

Discussion

Skin cutaneous melanoma(SKCM) is the most common subtype of melanoma and the deadliest form of skin cancer[13]. It is very aggressive and prone to metastases. At present, the treatment of SKCM is mainly surgery-assisted immunotherapy[14,15]. Many studies have reported that the prognosis of SKCM patients can be accurately predicted by constructing risk models of immune-related genes[4,16–18]. However, the disadvantage of immunotherapy is that the treatment effect is obviously related to individual differences, resulting in only a small number of patients benefiting. Therefore, it is necessary to explore molecular mechanisms other than immune mechanisms to provide new options for the treatment and diagnosis of SKCM. In recent years, some studies have revealed that ERS plays a certain role in the occurrence and progression of SKCM. Tumors primarily rely on the ability of preventing ERS-induced apoptosis and

interfering with ERS-related signaling to adapt to adverse external conditions for better survival[19]. Oxana et al[20] found that inhibition of ERS-induced autophagy sensitized melanoma cells to temozolomide treatment. Fan et al[21] reported that the low expression of ERS-related gene SERP1 was associated with poor prognosis in SKCM. In addition, due to the multiple mechanisms of lncRNA expression in cells, which can affect mRNA transcription and protein translation[22], more and more researchers were devoted to finding lncRNAs that can predict the prognosis of cancer patients[23,24]. A Studie had shown that LncRNAs play a role in the progression and metastasis of melanoma[16]. In this study, we analyzed the prediction of ERS-related lncRNAs on prognosis in SKCM patients and their impact on the tumor microenvironment.

First, we obtained 1613 ERS-related coding genes from GSEA, and then identified ERS-related lncRNAs by constructing an mRNA-lncRNA co-expression network. As a result, we obtained 14,142 ERS-related lncRNAs. Then, by univariate COX regression analysis we obtained 39 ERS-related lncRNAs, which were associated with the prognosis of SKCM patients ($p < 0.001$). Based on the consensus correlation of 39 ERS-related prognostic lncRNAs, we identified two subtypes of SKCM (cluster 1 and cluster 2). Compared to cluster 2, we found higher immune scores, stromal scores, and estimated scores in cluster 1. A previous study showed that bladder cancer patients with high levels of regulatory T cell infiltration had better overall survival[25]. In our study, we found that cluster 1 had a higher infiltrating abundance of T cells CD4 memory activated, T cells CD8, T cells follicular helper and Tcells regulatory (Tregs) than cluster 2, and cluster 1 had higher overall survival for cluster 2, which is consistent with previous studies.

Through GSEA pathway signal enrichment analysis of the two clusters, we found that cluster 2 was associated with Aminoacyl Trna biosynthesis and RNA polymerase. Cluster 1 was associated with chemokines, JAK-STAT signaling and natural killer NK cells. Many studies have shown that the JAK-STAT signaling pathway plays a role in biological processes such as cell division, apoptosis and immune regulation[26,27(p3)]. Apoptosis-inhibiting therapy is an important hallmark of SKCM. Survival analysis showed that patients with cutaneous melanoma in cluster 1 had better overall survival than those in cluster 2. Therefore, we guess that the JAK-STAT signaling pathway is more active in cluster 1 than in cluster 2.

LASSO Cox analysis was performed to construct a prognostic risk model consisting of 10 ERS-related prognostic lncRNAs. Based on risk scores, SKCM patients were divided into high-risk and low-risk groups. We found that patients with SKCM in the low-risk group had a better prognosis compared with the high-risk group. The features of 10 ERS-related lncRNAs have good discriminative performance for predicting the prognosis of SKCM patients, both in training cohort and in testing cohort. To our knowledge, our study is the first to use ERS-related lncRNA to construct a prognostic risk model for melanoma patients. Through bioinformatics analysis, Chen et al. identified 6 autophagy-related lncRNAs that can be used as prognostic biomarkers in melanoma[7]. Since ERS was a key factor leading to autophagy, it was reasonable to hypothesize that ERS-related lncRNAs may be associated with the prognosis of SKCM. In our study, we identified a prognostic signature based on 10 ERS-related prognostic lncRNAs. And through

univariate and multivariate Cox regression analysis, it was found that risk score can be used as an independent factor to predict the prognosis of SKCM patients.

By analyzing the association between prognostic risk scores and clinical characteristics in SKCM patients, we found that risk scores increased with increasing pT stage. Interestingly, the low immune score group had significantly higher risk scores than the high immune score groupv in our study. This finding was in contrast to findings from a previous study that showed that bladder cancer patients with a high immune score had poorer overall survival compared with those with a low immune score[28]. Contradictory results, which depend largely on how the tumor microenvironment differs across tumor types.

The important role of tumor immune microenvironment in tumorigenesis and progression has been reported in many literatures, and its heterogeneity can affect patient prognosis[29,30]. At the same time, studies had also revealed that the progression and metastasis of tumors and the prognosis of tumor patients were related to the level of immune cell infiltration [31,32]. In the present study, we found that the risk score increased with increased infiltration of M0 macrophages, M2 macrophages and mast cells resting. However, risk scores decreased with increased infiltration of B-cell memory, M1 macrophages, T-cell CD4 memory activation, T-cell CD8, and T-cell follicular helper. A study showed that M1 macrophages and M2 macrophages, which also have pro-inflammatory activity, have opposite effects on tumors, with M1 macrophages acting as an antitumor, while M2 macrophages can promote tumor growth[33]. It was consistent with our results. Our study revealed that higher levels of T-cell infiltration were associated with lower risk scores, implying better survival prognosis. This was also in line with findings from a previous study that showed better overall survival in bladder cancer patients with high levels of regulatory T cell infiltration[25]. By comparing the differences in gene expression levels of different immune checkpoints in high-risk and low-risk populations, we found that PD-L1, CTLA4, HAVCR2, LAG3, PDCD1 and VSIR were more highly expressed in low-risk populations. In addition, we also compared the sensitivity of high-risk group and low-risk group to different chemotherapy drugs, and found that the low-risk group was more sensitive to cisplatin and paclitaxel, and the high-risk group was more sensitive to sorafenib. Provide guidance for use. The results of PCA suggest that the significant differences between the high-risk and low-risk groups may be due to the different endoplasmic reticulum stress and oncogenic states induced by the risk model.

There are certain limitations in this study. First, the data established by lncRNA signatures come from public databases, and the classification effect of lncRNA signatures needs to be verified experimentally. To further validate our predictions, in-depth functional experimental exploration of the 10 ERS-related lncRNAs is necessary.

Conclusion

In conclusion, this study constructed a clinicopathological-independent prognostic signature constructed from 10 ERS-related lncRNAs based on data from SKCM patients in the TCGA database. Through

consensus clustering of ERS-related prognostic lncRNAs and construction of a prognostic risk model, we analyzed the impact of ERS-related lncRNAs on the prognosis of SKCM patients and their important roles in the immune microenvironment. This study is the first to report that ERS-associated lncRNA signatures can predict prognosis and immunotherapy response in human SKCM. Our risk model provides new potential biomarkers for prognosis and treatment selection in SKCM. It also gives us a deeper understanding of the important role of lncRNAs in SKCM.

Declarations

Ethics approval and consent to participate

Our study has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Nanchang University

Consent for publication

Our manuscript contains not any individual data in any form.

Conflict of interest

There is no conflicts of interest to declare for any of the authors.

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Authors' contributions

Interpretation or analysis of data: An-an Li

Preparation of the manuscript: An-an Li

Revision for important intellectual content: Mei-ying Yang

Data availability statement

The datasets analyzed in this study can be found in this paper. Raw counts for RNA-seq transcriptome data and corresponding clinical data for skin cutaneous melanoma were extracted from TCGA (https://portal.gdc.cancer.gov). ERS-related genes were extracted from GSEA(https:/ /www.gsea-msigdb.org/gsea/index.jsp).

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Tables

Table 1. Clinical pathological parameters of patients with SKCM

Feature	N (321)	%
Gender		
female	123	38.3
male	198	61.7
Age□years□		
≤65	204	63.6
□65	117	36.4
TNM stage		
I	71	22.1
II	118	36.8
III	123	38.3
IV	9	2.8
T classification		
T1	37	11.5
T2	69	21.5
T3	83	25.9
T4	132	41.1
M classification		
M0	312	97.2
M1	9	2.8
N classification		
N0	197	61.4
N1	58	18.1
N2	31	9.6
N3	35	10.9

Note: T, tumour size; N, lymph node; M, distant metastasis; TNM stage, according to AJCC classification; SKCM, skin cutaneous melanoma.

Table 2. The risk model of 10 ERS-related prognostic lncRNAs in SKCM by Lasso regression analysis.

lncRNA	Coef
AATBC	0.051453983
ZEB1-AS1	-0.276339388
LINC01871	-0.117565013
AC093726.1	-0.003753367
AC021188.1	-0.101140404
AC092747.4	-0.017287994
AC009495.2	0.142462615
AL157871.2	-0.044616
AC242842.1	-0.067446679
AC067930.4	-0.126903496

Note: ERS, endoplasmic reticulum stress; skcm, skin cutaneous melanoma; Coef, Correlation coefficient.

Figures

Figure 1

Identification of ERS-related lncRNAs with significant prognostic value in SKCM. (A) The forest showed the HR (95% CI) and p-value of selected lncRNAs by univariate Cox proportional hazards analysis. (B) The heatmap showed expression levels of selected lncRNAs in normal and tumor tissues by univariate Cox proportional hazards analysis (C), the correlation between 39 lncRNAs and PD-L1

Figure 2

Consensus clustering of ERS-related prognostic lncRNAs. (A) TCGA SKCM cohorts were grouped into two clusters according to the consensus clustering matrix (k =2). (B) Overall survival analysis revealed a better overall survival of bladder cancer patients in cluster 2 compared with that in cluster 1. (C) The heatmap of the two clusters along with clinicopathological characteristics.

Figure 3

The correlation between two clusters and immune cell infiltration in SKCM. (A–C) SKCM patients in cluster 1 had a higher immuneScore, stromalScore, and ESTIMATEScore compared with those in cluster 2. (d)The infiltrating levels of 22 immune cell types in cluster1/2 subtypes in SKCM.

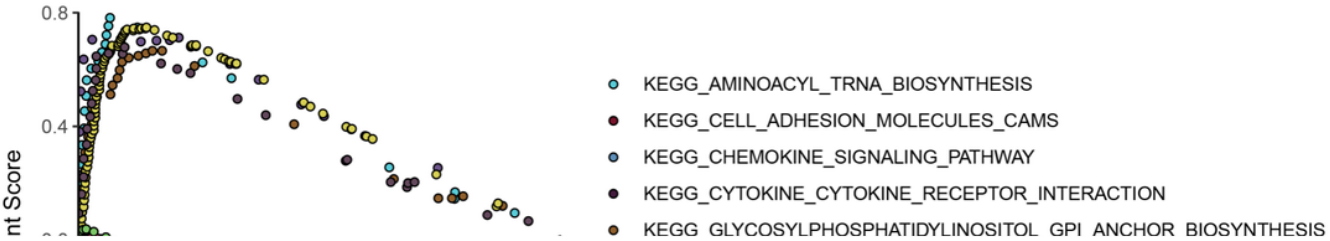

Figure 4

Gene set enrichment analysis of ERS-related prognostic lncRNAs in the cluster1/2 subtypes.

Figure 5

The construction of a prognostic risk model by using LASSO regression. (A) LASSO coefficient profiles of the 10 prognostic lncRNAs. (B) Plots of the cross-validation error rates.

Figure 6

Distributions of 10-lncRNA expression, signature score, survival status and survival probability for patients in high-risk and low-risk groups. (A-D) Train cohort; (E-H) Test cohort.

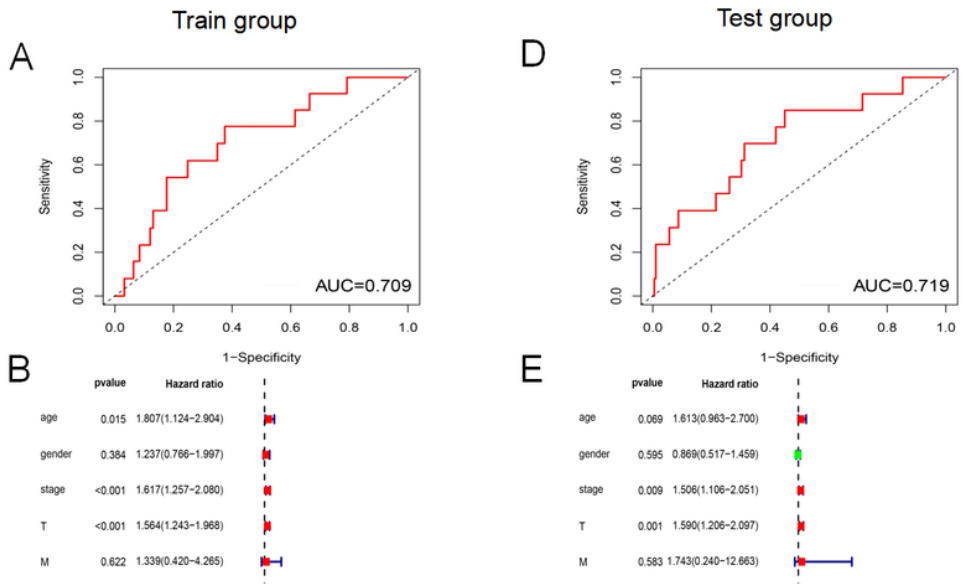

Figure 7

Independent predictive power and accuracy of the lncRNA signature in SKCM patients. (A/D), AUC values for risk score in train group(A) and test group(D); (B/E) Univariate Cox analysis in train cohort (B) and test cohort (E). (B) Multivariate Cox analysis in train cohort (C) and test cohort (F).

Figure 8

Validation of prognostic risk models and clinicopathological characteristics of patients in high-risk and low-risk groups. The heatmap of both high-risk group and low-risk group among with clinicopathological characteristics;

Figure 9

Correlation of risk score with immune cell infiltration and expression of different immune checkpoint molecules, and the sensitivity of patients in high-risk and low-risk groups to different chemotherapy drugs. (A-H) Scatter plots showing the significant correlation of 8 kinds of immune cells with risk score; (I-K); Differences in sensitivity to cisplatin(I), paclitaxel(J) and sorafenib(K) in high-risk and low-risk groups; (L-Q) The differential expression of PDL-1(L), CTLA4(M), HAVCR2 (N), LAG-3 (O), PDCD1(P), and VSIR (Q) between the high-risk and low-risk groups.

Supplementary Files

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