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Research Article

LINC01224, AC015849.16, and LINC00908 as Novel Prognostic Signatures in Clinical Stage-Wise Uterine Corpus Endometrial Carcinoma (UCEC)

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Abstract

Objectives: Uterine corpus endometrial carcinoma (UCEC) is a malignant cancer that exhibits significant molecular heterogeneity, leading to distinct clinical outcomes. The aim of this study is to identify long non-coding RNAs (lncRNAs) with independent and superior prognostic value based on the tumor clinical stages in UCEC patients.

Methods: The Cancer Genome Atlas (TCGA) was utilized to acquire clinical data and expression levels of lncRNAs and mRNAs in UCEC patients. Tumor samples were compared with normal samples using R-statistical computing and Cytoscape. Four lncRNA-expression signatures (LINC01224, AC015849.16, LINC00908, and LINC00092) were identified through tenfold cross-validation, t-tests, and univariate COX regression.

Results: LINC00908 and LINC00092 exhibited a negative correlation with tumor stages and were downregulated in expression compared to normal samples. Conversely, LINC01224 and AC015849.16 were upregulated in tumor samples and positively correlated with the overall survival of UCEC patients. The lncRNAs-mRNAs network and functional enrichment analysis indicated the involvement of these four lncRNA signatures in UCEC tumor progression by modulating pathways such as TGF-β signaling, cell cycle, DNA replication, NF-kB signaling, and Notch signaling.

Conclusion: LINC01224, AC015849.16, LINC00908, and LINC00092 could be considered as alternate prognostic markers for UCEC prediction, potentially improving overall survival and enabling patient-tailored treatment strategies.

Keywords: Uterine corpus endometrial carcinoma, prognosis, lncRNAs, tumor progression, overall survival

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Uterine corpus endometrial carcinoma (UCEC) is one of the most common female reproductive system tumors, which originates from the inner lining of the uterus.[1] UCEC ranks the 6th most commonly diagnosed cancer in women, with incidence of 417,000 new cases and 97,000 deaths in 2020, and ranks the 3rd most common gynecological malignant tumor that causes death after ovarian cancer and cervical cancer.[2] The 5-year survival rate of the

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patients diagnosed with UCEC has been reported to be minimal, especially in the patients who have been experiencing tumor metastasis after surgery or radiotherapy.[3-7] There is a need to improve both prognostic strategies and new treatment modalities to enhance the overall survival in UCEC patients particularly those with recurrent metastasis. Therefore, it is necessary to identify novel prognostic biomarkers for the prognosis of UCEC patients in order to choose personalized therapy.[8]

Long non-coding RNAs (lncRNAs) are transcripts composed of more than 200 nucleotides, which cannot code for a protein. These are involved in multiple functions such as, signaling, decoying, scaffolding, and guidance.[9-14] Recent studies have demonstrated the important role of lncRNAs in modulating the tumor proliferation, invasion, prognosis, and metastasis.[15,16] A plethora of scientific reports delineated the implications of several lncRNA signatures to predict the overall survival of the patients during several cancers.[17-22] LINC01224 is involved in the progression of endometrial carcinoma through the miR-485-5p/AKT3 signaling sugegsting its role as a diagnostic marker.[23] Another report by Jin Y et al described a significant correlation of lncRNA MALAT1 with the proliferation and metastasis in epithelial ovarian cancer.[24] A few reports described the dysregulated expression of lncRNAs in UCEC due to their differential expression.[25-27] However, there are relatively few studies on lncRNA transcriptome data analysis to screen tumor stage-related biomarkers for UCEC patients.

In this study, we screened prognostic significance of lncRNAs as biomarkers related to tumors of different clinical stages through tenfold cross-validation by using TCGA data pertinent to UCEC patients. Four lncRNAs related to normal tissue and tumor tissue of different stages were determined according to our pipeline. Then we performed a lncRNA-mRNA co-expression network through the analysis of correlations between these four lncRNAs and mRNAs. Finally, we conducted KEGG pathway and GO analysis to understand the potential mechanisms of these four lncRNAs.

Methods

Data Source

High-throughput RNA sequencing expression profiles including lncRNA and mRNA and their correlated clinical data pertinent to the patients with UCEC were download from the Cancer Genome Atlas (TCGA: UCSC Xena- http://xena.ucsc.edu). Data collection was performed from the TCGA database. We have not received any third party support in conducting this research, analyzing the data, or preparing the manuscript for submission. Total 583 UCEC patients with survival outcomes were selected from TCGA, and then we eliminated patient data without a clear pathological grade or clinical information. Clinical information pertinent to gender, age, and pathological stage was obtained from the UCSC Xena. Finally, the expression data and correlated clinical information of 548 UCEC patients, including 341 grade I, 51 grade II, 127 grade III and 29 grade IV, and 23 normal adjacent samples were included in this study. It is worth noting that exchanging the Accession number to the ID of lncRNA and mRNA was performed by the GENCODE database (https://www.gencodegenes.org/).

Data Processing

Primarily, we selected differentially expressed lncRNAs in cancer and normal samples of UCEC using the limma package (http://bioconductor.org/packages/release/bioc/html/limma.html) by cut-off parameters FDR<0.05, |Log2FC| >2. Subsequently, we performed Spearman correlation coefficients ($p<0.05$) for exploring the correlations between the lncRNAs and clinical stage by using cor.test (). In order to avoid random allocation bias that may affect the stability exhibited by subsequent signatures, we applied tenfold cross-validation for the selection of lncRNAs, and the data were randomly divided into ten different sets. In the tenfold cross-validation, nine sets were used for training, and the remaining set was used for validation. Later, we selected the 'lncRNAs that were negatively correlated with the UCEC stage and increased in normal tissues'; and subsequently deciphered the 'positive correlation of lncRNAs () with the UCEC stages but decreased in normal tissues'. Furthermore, Cytoscape software was used in constructing lncRNA-mRNA interaction networks for the identification of GO enriched terms and KEGG pathways. Clusterprofiler package was used to carry out this analysis (Fig. 1).

Data Analysis

Statistical analyses were performed using the R software 3.5.0. The p-values of less than 0.05 were considered as statistically significant. The overall survival was deciphered using Kaplan-Meier analysis and the group comparisons were performed with the aid of a log-rank test. Forest plots assisted in order to screen the lncRNAs related to prognosis. Univariate and multivariate Cox regression analyses were employed to determine lncRNAs associated with patient's overall survival.

Results

Patient Characteristics in UCEC

In this study, a total of 15251 lncRNAs were obtained from 571 samples which include 23 normal samples and 548 tumor samples in the TCGA database. A total of 548 tumor samples were identified, and the baseline clinical characteristics were given in the following Table 1.

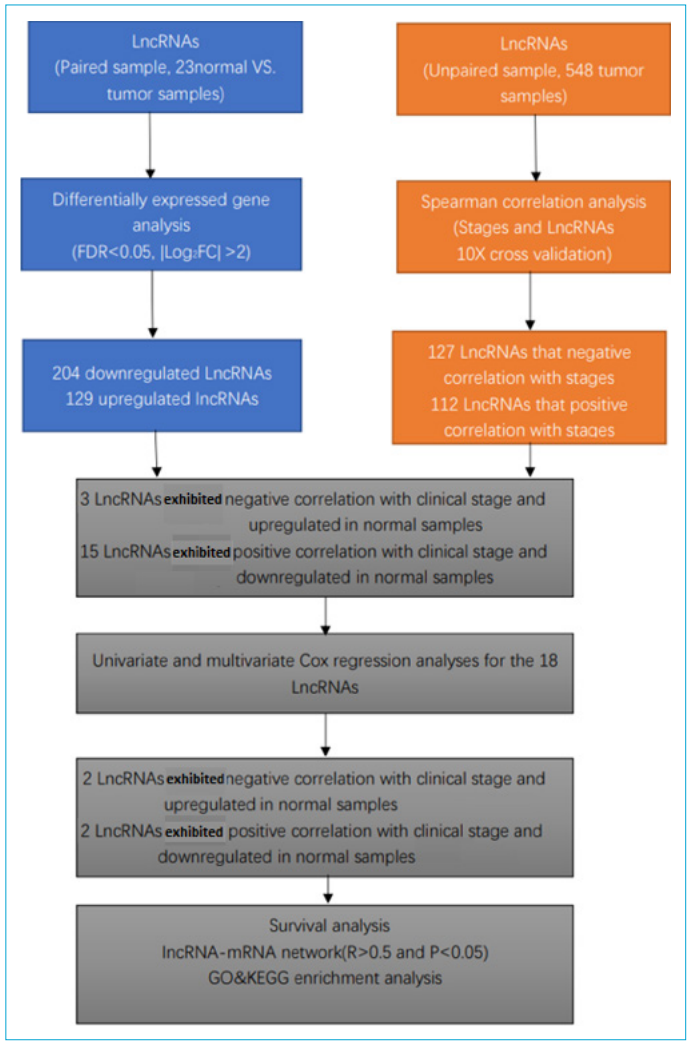

Figure 1. Flowchart for overall study design.

Screening Differentially Expressed lncRNAs in UCEC Patients

The limma algorithm was applied to screen the differentially expressed lncRNAs in the tumor samples when compared to normal samples. The results showed that 204 lncRNAs and 129 lncRNAs were downregulated and upregulated in tumor samples respectively when compared to the matched normal samples (Fig. 2A-C).

LncRNAs were Associated with the Clinical Staging of UCEC Patients

The tenfold cross-validation was performed and ascertained the lncRNAs. Among them, two lncRNAs such as LINC01224 and AC015849.16 exhibited a negative correlation with clinical stage and upregulated in its matched normal samples. On the contrary, another two lncRNAs such as LINC00908 and LINC00092 exhibited a positive correlation with clinical stage and downregulated in its matched normal samples. The four significant overall survival-related

Table 1. Baseline clinical characteristics of uterine corpus endometrial carcinoma (UCEC) patients obtained from TCGA database.

Stage	Stage1 (n=341)	Stage 2 (n=51)	Stage 3 (n=127)	Stage 4 (n=29)
Age				
<65	185	31	75	15
≥65	156	20	52	14
Race				
White	245	33	81	17
Asian	14	2	3	1
Black	61	13	37	9
NA	21	3	6	2
Grade				
G1	82	4	12	0
G2	87	13	19	1
G3	168	34	92	25
G4	4	0	4	3
Hypertension				
Yes	142	24	57	9
No	104	10	36	12
NA	95	17	34	8
Diabetes				
Yes	61	9	23	7
No	171	26	58	13
NA	109	16	46	9
BMI				
18.5-24.9	60	9	21	7
25-29.9	71	8	31	4
30-39.9	112	20	45	14
≥40	80	11	20	3
NA	18	3	10	1

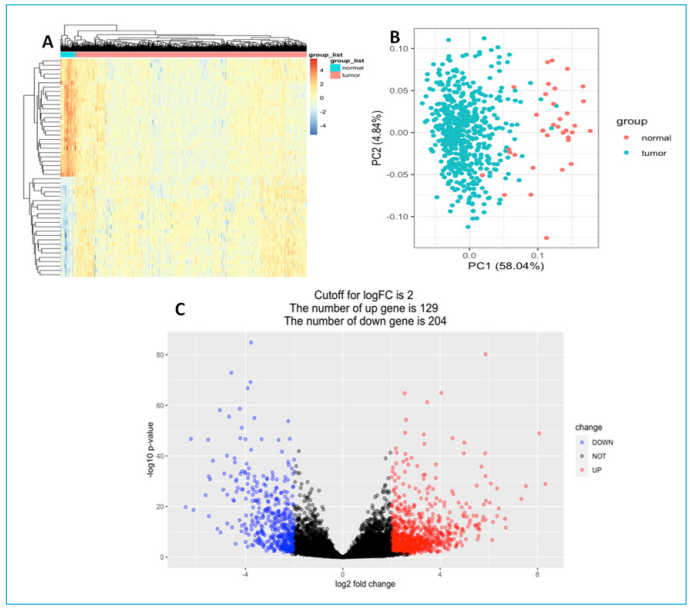

Figure 2. (a, b) Heatmap and Principal Component Analysis (PCA) of the top 50 differentially expressed lncRNAs between normal and tumor samples; **(c)** volcano plot of differentially expressed lncRNAs.

lncRNAs were obtained from the analysis of the lncRNAs by univariate COX regression (Fig. 3A). According to our result, two lncRNAs (LINC00908 and LINC00092) were observed to be downregulated than normal samples and these lncRNAs were negatively correlated with clinical stage. Two lncRNAs (LINC01224 and AC015849.16) were upregulated than normal samples and these lncRNAs were positively correlated with clinical stage (Fig. 3B-3E).

We highlighted a total of 4 lncRNAs among 18 lncRNAs with specific correlation to the overall survival through univariate and multivariate Cox regression analyses (Table 2). The upregulated lncRNAs such as LINC01224 and AC015849.16 were positively correlated to poor overall survival with statistical significance ($p<0.05$) through multivariate analysis. LINC00092 was downregulated but typically exhibited specific statistical significance with overall survival.

Prognostic Overall Survival Assessment of lncRNAs

We performed the survival analysis to evaluate the prognostic significance of four lncRNAs based on TCGA data and clinical information. We found that the patients typically with higher expression levels of LINC01224 and AC015849.16 reported low overall survival. The patients with a higher expression of LINC00908 were associated with poor overall survival rate. However, there was no significant correlation between the expression of LINC00092 and UCEC prognosis ($p>0.05$). All survival analysis results were given in Figure 4A-D.

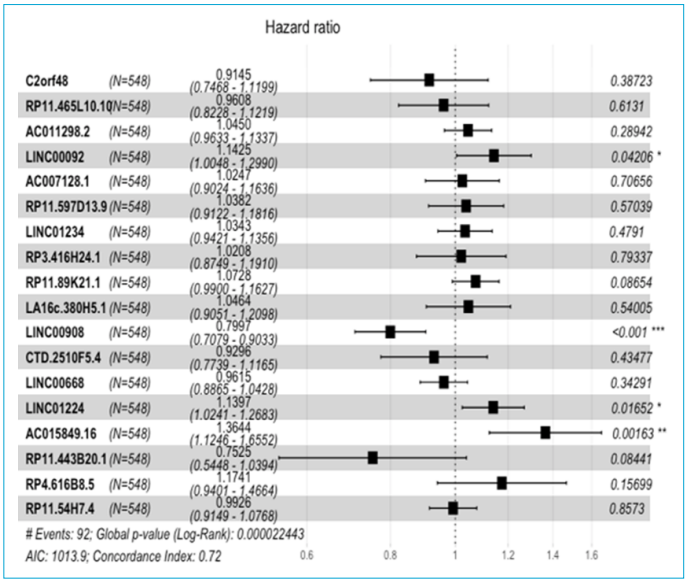

Figure 3. (a) Univariate Cox regression analysis with the lncRNAs, the top four significant factors with $p<0.005$; **(b-e)** The correlation of lncRNAs expression with clinical stages of stage I to stage IV compared to normal. Student t-test was used for testing the statistical significance.

Table 2. Univariate and multivariate Cox regression analyses of the 18 lncRNAs associated with overall survival in UCEC. Importance of total 4 lncRNAs among 18 lncRNAs with specific correlation to the overall survival was described in this study (highlighted in red).

Ensembl id	Gene symbol	Genomic location	Univariate			Multivariate		
			HR	95%CI	p	HR	95%CI	p
ENSG00000171848	C2orf48	chr 2: 10,120,698-10,211,725	1.23	1.07 - 1.41	0.003	0.914	0.747 - 1.12	0.387
ENSG00000204044	RP11.465L10.10	chr 20: 46,013,500-46,022,073	1.07	0.94 - 1.23	0.293	0.961	0.823 - 1.122	0.613
ENSG00000219159	AC011298.2	chr 2: 240,686,334- 240,690,414	1.12	1.05 - 1.2	0.001	1.045	0.963 - 1.134	0.289
ENSG00000225194	LINC00092	chr 9: 96,019,724-96,027,993	1	0.89 - 1.13	0.998	1.142	1.005 - 1.299	0.042
ENSG00000229970	AC007128.1	chr 7: 8,262,264- 8,344,516	1.16	1.04 - 1.29	0.01	1.025	0.902 - 1.164	0.707
ENSG00000248429	RP11-597D13.9	chr 4:158170752- 58202877	0.93	0.83 - 1.04	0.192	1.038	0.912 - 1.182	0.57
ENSG00000249550	LINC01234	chr 12: 113,583,886-113,773,726	1.13	1.05 - 1.21	0.001	1.034	0.942 - 1.136	0.479
ENSG00000257671	RP3-416H24.1	chr 12: 52,245,048- 52,247,448	1.22	1.08 - 1.39	0.002	1.021	0.875 - 1.191	0.793
ENSG00000259439	RP11-89K21.1	chr 2: 44,921,077- 44,939,199	1.12	1.05 - 1.2	0.001	1.073	0.99 - 1.163	0.087
ENSG00000262152	LA16c.380H5.1	chr 16: 2,988,256-3,002,016	1.17	1.05 - 1.3	0.004	1.046	0.905 - 1.21	0.54
ENSG00000266256	LINC00908	chr 18: 76,528,652-76,670,111	0.85	0.77 - 0.94	0.002	0.8	0.708 - 0.903	0
ENSG00000265415	CTD-2510F5.4	chr 17: 59,202,677- 59,203,829	1.19	1.04 - 1.36	0.013	0.93	0.774 - 1.117	0.435
ENSG00000265933	LINC00668	chr 18: 6,919,496-6,929,966	1.08	1.01 - 1.15	0.029	0.961	0.886 - 1.043	0.343
ENSG00000269416	LINC01224	chr 19: 23,399,097-23,416,075	1.21	1.11 - 1.31	0	1.14	1.024 - 1.268	0.017
ENSG00000270977	AC015849.16	chr 17:35,893,707-35,911,023	1.35	1.19 - 1.54	0	1.364	1.125 - 1.655	0.002
ENSG00000271936	RP11-443B20.1	chr 2:24,825,610-24,826,717	1.33	1.1 - 1.61	0.003	0.752	0.545 - 1.039	0.084
ENSG00000274825	RP4-616B8.5	chr 20:38,955,910-38,956,547	1.28	1.09 - 1.5	0.003	1.174	0.94 - 1.466	0.157
ENSG00000275216	RP11-54H7.4	chr 13:109,269,634-109,273,838	1.08	1.01 - 1.15	0.021	0.993	0.915 - 1.077	0.857

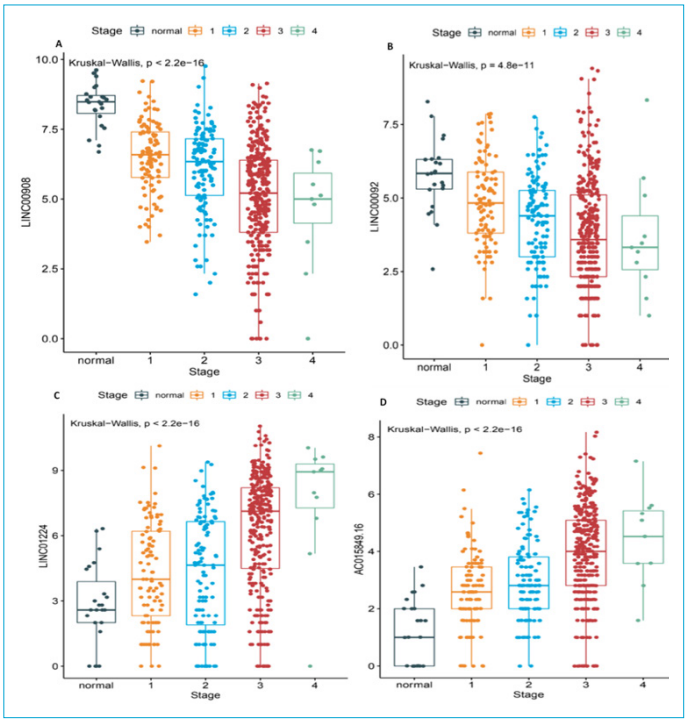

Figure 4. Overall survival analysis of LINC01224 **(a)**, AC015849.16 **(b)**, LINC00908 **(c)** and LINC00092 **(d)** by the Kaplan-Meier curves.

LncRNA-mRNA Network Construction

In order to explore the connection between lncRNAs and mRNAs in the progression of UCEC, we obtained mRNAs which were closely related to the four lncRNAs by using the Spearman correlation method according to R>0.5 and p<0.05. Based on the obtained lncRNAs and mRNAs correlations, the lncRNA-mRNA interaction relationship was constructed by applying Cytoscape software. According to this lncRNAs-mRNAs network (Fig. 5), it has been observed that LINC0908 is concatenated with LINC00092, which can influence mRNAs expression including ZDHHC1, ERICH3 and C9orf9; LINC01224 is concatenated with AC015849.16, which can influence ESPL1,TPX2, TTK, and MTBP expression.

GO and KEGG Enrichment Analysis of mRNAs

Gene ontology (GO) and KEGG enrichment analysis was carried out to delineate the significant implications of mRNAs with the four lncRNAs for characterizing the potential mechanisms of the four lncRNAs such as LINC00908 and LINC00092, LINC01224 and AC015849.16. Enrichment analysis showed that mRNAs were highly enriched not only in TGF-beta signaling pathway, cell cycle, DNA replication, NF-kappa B signaling pathway and Notch signaling pathway in KEGG, but also in DNA helicase activity and DNA-dependent DNA replication in GO (Fig. 6A, 6B).

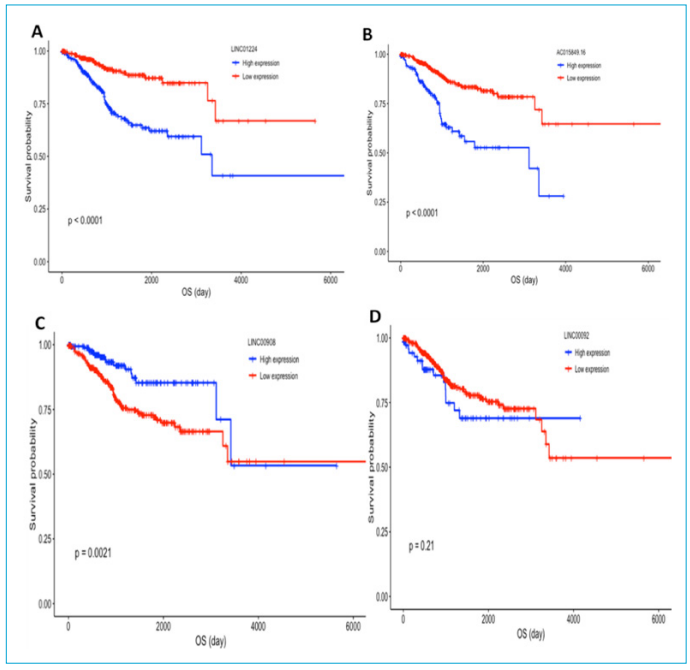

Figure 5. The lncRNAs-mRNAs network constructed with R>0.5 and P<0.05; red indicates interacting lncRNAs such as LINC00908 and LINC00092 through mRNAs include, ZDHHC1, ERICH3 and C9orf9 whereas green stands for interacting lncRNAs such as LINC01224 and AC015849.16, through mRNAs such as ESPL1, TPX2, TTK, and MTBP.

Discussion

UCEC is the most common gynecologic malignancy in women and over 50,000 women died of UCEC every year around the world 28. The rapid development of radiotherapy and chemotherapy led to the improved cure rate of UCEC patients over the past few decades, but a lot of patients are still unable to receive effective treatment due to the advanced stages of UCEC at initial diagnosis. Therefore, it is crucial to explore the effective prognostic biomarkers and underlying biological mechanisms in the development of UCEC in order to improve patient's clinical outcomes. In the current study, we used the TCGA database to decipher differentially expressed lncRNAs across different clinical stages in UCEC patients in order to predict the prognosis of UCEC patients. In addition, GO and KEGG enrichment analysis was conducted to analyze the lncRNAs-mRNAs network to understand the intrinsic role of these lncRNAs in tumor progression. Previous findings have demonstrated the important role of lncRNAs in various biological processes including tumor progression. For instance, Zhang DM et al. indicated the involvement of lncRNA H19 in the progression of tongue squamous cell carcinoma through association with EZH2, and affects downstream β-Catenin/GSK3β/EMT signaling.[29] LINC00944 is another lncRNA reported to be associated with the prognosis of breast cancer by targeting the ADAR1.[30] A previous study by Meng Zhou et al. (2018)

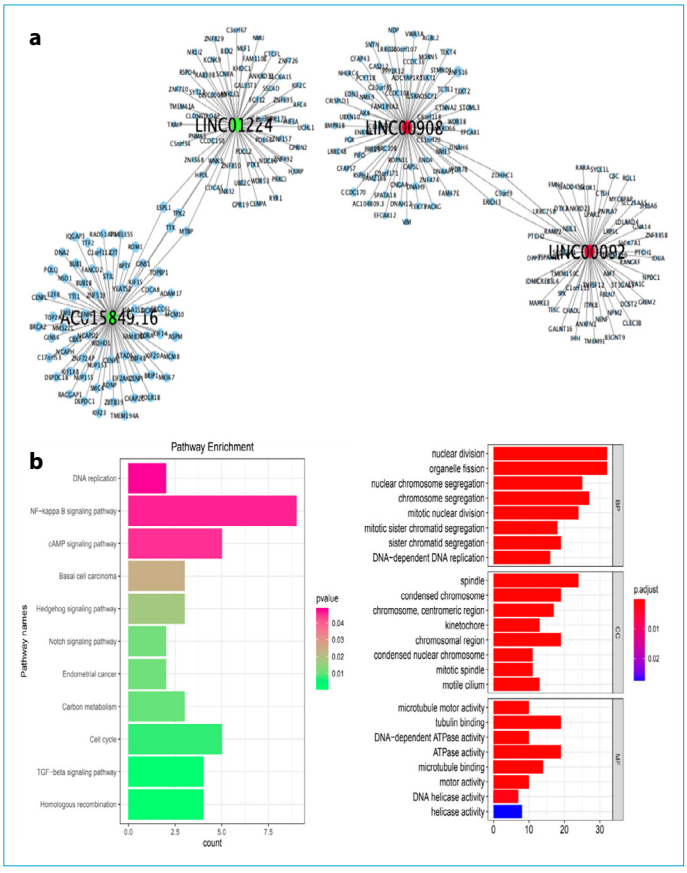

Figure 6. (a, b) The enrichment scores for biological processes in KEGG and GO enrichment. The enriched biological processes and signaling pathways pertinent to protein-coding genes were correlated with prognostic lncRNAs in the signature. LINC00908 and LINC00092, LINC01224 and AC015849.16 and their target mRNAs were involved in modulating several signaling pathways to enhance UCEC progression.

described 11 lncRNAs signature as independent prognostic lncRNAs such as 'RP11-1072A3.3.1, ACVR2B-AS1, RP4-781 K5.7.1, AC073046.25, AP001347.6, DOCK9-AS2, NRAV, GTF3C2-AS1, LINC01006, RP11-531A24.5 and AC004947.2' for predicting overall survival of UCEC patients.[7] A study by Yi Yuan et al. 2021 described the higher expression of three lncRNAs AC015849.16, DUXAP8 and DGCR5 in UCEC tumors when compared to nontumor tissue subsequently concluded their negative correlation to five-year overall survival.[31]

As described by the previous reports, LINC01224 is involved in carcinogenesis as it can induce cancer cell proliferation in tumors subsequently fostering invasion, migration. This lncRNA is upregulated along with tumor grade and associated with poor prognosis in epithelial ovarian cancer.[23, 32, 33] LINC00908 could encode 'automatic speech recognition and processing server' (ASRPS), a small regulatory peptide reported to be downregulated in triple negative breast cancers. This peptide can typically interact with STAT3 by coiled-coil domain and impair the phosphorylation of STAT3 subsequently induce the inhibition of VEGF expression.[34, 35] Upregulated expression of LINC00092 is observed in metastatic ovarian cancer and is associated with poor prognosis for this cancer. In addition, this lncRNA could foster the cancer associated fibroblast (CAF)-mediated ovarian cancer progression through the modulation of glycolytic cycle by direct interaction with 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-2 (PFKFB2) in these cancer cells.[36-38] For instance, the CAF-generated CXCL14 could promote change in the expression patterns of LINC00092 in ovarian cancers and subsequently enhance tumor growth.[36, 39]

In our study, four lncRNAs (LINC01224, AC015849.16, LINC00908 and LINC00092) were identified with significant correlation across different clinical stages of tumor tissue and normal tissue in UCEC patients. The expression levels of LINC01224 and AC015849.16 have been increasing with the tumor stages of UCEC and the higher expression of these lncRNAs exhibited a significant relationship with poor prognosis than normal samples. But the expression pattern of LINC00908 and LINC00092 typically decreases with the 'tumor stage' of UCEC and increases in the normal samples. Recent reports have concluded that the silencing of LINC01224 could inhibit the development of hepatocellular carcinoma by downregulating the expression of CHEK1 via miRNa-330-5p 40. Fan L et al. confirmed that LINC00908 can increase the expression of TSPYL5 by competitive binding to miR-483-5p, which played a vital role in prostate cancer, due to its ability to inhibit invasion and migration of cancer cells.[41, 42] As described above, Zhao L et al. revealed that the LINC00092 is associated with CXCL14 expression and involved in modulating metastasis and prognosis of ovarian cancer.[43] In our study, overall survival analysis for these lncRNAs showed that LINC01224, AC015849.16 and LINC00908 correlated to the prognosis in patients with UCEC. Therefore, LINC01224, AC015849.16 and LINC00908 could be considered as novel biomarkers for significant prognosis and metastasis of UCEC. Expression of certain lncRNAs and their target mRNAs could be negatively regulated in a lncRNA-mRNA regulatory module.[44] LncRNAs located at the upstream promoter region of the coding gene can foster the impairment of adjacent gene expression. Trans-acting lncRNAs could function through the modulation of proteins or RNAs with direct binding.[44]

To further explore the correlations between these four lncRNAs, we identified several mRNAs that were associated with these lncRNAs through lncRNA-mRNA coexpression network. Interestingly, we found that the LINC01224 expression is linked to AC015849.16 through ESPL1, TPX2, TTK and MTBP. Among these mRNAs, Gurvits Net al. report-

ed that ESPL1 expression can enable to predict the prognosis of breast carcinoma in the patients by ascertaining the separase expression.[45] Overexpression of TPX2 (Targeting Protein for Xenopus Kinesin Like Protein 2) has been reported in breast cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, and non-small cell lung cancer. Chen M et al showed that the silencing of TPX2 prevented the proliferation of breast cancer cells by regulating the PI3K/AKT and activating p53 signaling pathway.[46] Another study by Huang DH et al found that TPX2 downregulation may inhibit the growth of hepatocellular carcinoma via the PI3K/AKT signal transduction pathway.[47] Tian Y et al confirmed that the targeted silencing of TPX2 reduced cell proliferation of ovarian cancer by negatively regulating the AKT signaling pathway.[48] Threonine and tyrosine kinase (TTK) was also considered as a biomarker for prognosis in multiple cancers 49-51. Chen J et al. reported that it is possible to be a potential therapeutic target and biomarker for the prognosis of NSCLC.[52] MDM2 Binding Protein (MTBP) plays a vital role in the regulation of tumor invasion and metastasis of breast cancer,[53] hepatocellular carcinoma,[54] and squamous cell carcinoma of the head and neck.[55] A report by Shijin Huang et al. 2021 described that genes such as BUB2, NDC80, TPX2, and TTK are reported to be involved in the cell cycle and independently associated with the prognosis of EC.[56] For instance, the differential expression of TPX2 could have significant implications in overall survival in EC patients. Another study by Yi Yuan et al 2021 described that the genes such as AURKA, BUB1, CDCA8, DLGAP5, KIF2C and TPX2 could be involved in the pathogenesis of UCEC and these genes have significant role in the cell cycle, DNA replication, and mismatch repair.[31] TPX2 could be considered as the potential biomarker due to its prognostic relevance in EC.[57] In addition, the TTK is another gene associated with prognostic relevance in EC and it is a protein kinase which mediates the phosphorylation of proteins at serine, threonine, and tyrosine pertinent to cell proliferation, mainly for mitotic checkpoint.[56] High expression of TTK is associated with poor prognosis for cancers such as EC, liver cancer, and pancreatic cancer.[56, 58-60] Another study by Qiannan Yang et al. 2020 described the prognostic relevance of TTK, CDC25A, and ESPL for EC.[60] Our results are consistent with those studies. By performing enrichment analysis, we inferred that the four lncRNAs might promote cancer cell growth, migration and invasion by TGF-β signaling pathway, cell cycle, DNA replication, NF-kB signaling pathway and Notch signaling pathway. We showed that the LINC00908 expression is linked to LINC00092 through ZDHHC1, ERICH3 and C9orf9. However, the mechanism of these three mRNAs in different types of cancer still requires additional studies.

Conclusion

In summary, our study performed a series of analyses and defined four lncRNAs such as LINC01224, AC015849.16, LINC00908 and LINC00092 related to tumor stages of I to IV in UCEC patients. The role of these lncRNAs is described in the tumor progression of UCEC by integrating results obtained through lncRNAs-mRNAs network, overall survival, and enrichment analysis. We identified LINC01224, AC015849.16 and LINC00908 are highly associated with the prognosis of UCEC, which provides new insight into the diagnosis and choosing suitable therapeutic strategies to target UCEC at an early stage. This study provided a novel genetic landscape and the foundation for prognostic prediction or for more effective treatment of UCEC.

Disclosures

Ethics Committee Approval: Data collection was performed from the TCGA: UCSC Xena- http://xena.ucsc.edu database; the data acquired from this database was completely with authorized approval of committee of First affiliated hospital of Zhengzhou University for further analysis. We have not received any third party support in conducting this research, analyzing the data, or preparing the manuscript for submission. Hence, our study does not require any ethical approval statement.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – N.M.B., R.F., J.L., S.Z.; Design – R.F., J.L., N.M.B.; Supervision – R.F., J.L., N.M.B.; Materials – S.Z., Y.Z., F.Z., C.Z., N.X., P.M.; Data collection &/or processing – N.M.B., S.Z., K.V.B., V.N.N., J.L., R.F.; Analysis and/or interpretation – S.Z., N.M.B.; Literature search – N.M.B., S.Z.; Writing – N.M.B.; Critical review – N.M.B., R.F.

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