Research Article

Journal of Bioscience & Bioengineering

Comprehensive analysis of cuproptosis-related LncRNA and prognosis, immune function and potential drug screening in endometrial carcinoma

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Received Date: 15 Dec 2023
Accepted Date: 10 January 2024
Published Date: 15 January 2024

Citation:
Jianqian Tong and Xi Cheng. Comprehensive Analysis Of Cuproptosis-Related Lncrna And Prognosis, Immune Function And Potential Drug Screening In Endometrial Carcinoma.
Journal of Bioscience & Bioengineering 2024.

1. Abstract

Endometrial cancer (EC) is the sixth most common cancer among women worldwide. Although the overall survival (OS) of early-stage EC is relatively high, the prognosis of patients with advanced or recurrent EC is still very poor. Therefore, the novel therapeutic targets of EC need to be explored urgently. To explore the prognostic value ofcuproptosis-related lncRNAand its correlation withimmune-related functions and drug screening in EC. First, we download EC-related data from The Cancer Genome Atlas (TCGA) database. Then, a prognostic modelof cuproptosis-related lncRNA (12-lncRNAs model) was constructed. Third, the model was verified and analyzed. In our study, the prognosis was worse for high-risk patients than for low-risk patients. The patients with high tumor mutational burden (TMB) and low 12-lncRNAs expression had the best prognosis. 12-lncRNAs model was linked to the immune functions ofType I IFN Response and Parainflammation (PI).13 drugs were screened by 12-lncRNAsmodel. In summary, these lncRNAs might be potential therapeutic targets for EC treatments, thereby providing new ideas against EC.

2. Keywords:
Cuproptosis; LncRNA; TCGA; Tumor mutational burden; Endometrial cancer; Survival; Treatment; Drug; Immune function;

3. Introduction

Globally, endometrial cancer (EC) is the sixth most common cancer in women, which is an epithelial malignancy occurring in the endometrium. In the past few years, EC has shown an increasing trend in global morbidity and mortality [1]. In 2020, an estimated 417,367 women were diagnosed with EC worldwide, with the highest number of cases in North America and Western Europe [2]. According to the Global Cancer Observatory (GCO), there were an estimated 97,370 deaths in 2020 [3]. The overall survival (OS) of early-stage EC was relatively high, but the prognosis of patients with advanced or recurrent EC was still very poor. The 5-year OS of stage IVA and IVB EC were only 17% and 15%respectively [4]. Historically, EC has been divided into two main clinicopathological and molecular types: Type I as estrogen-dependent endometrioid adenocarcinomas (EAC) (80%-90%) and Type II includes non-endometrioid subtypes such as serous, clear cell and undifferentiated carcinomas, as well as carcinosarcoma/malignant mixed Müllerian tumor (MMMT) (10%-20%) [5]. Total hysterectomy and bilateral salpingo-oophorectomy were the main treatments for EC, but patients with advanced-stage/metastasis could not be cured by current treatment strategies [6]. Therefore, it is urgent to explore novel targets for EC therapy.

Cell death is a fundamental, finely-tuned process that is essential for the removal of damaged and excess cells. To date, various forms of

programmed and non-programmed cell death have been found, including apoptosis, ferroptosis, and necroptosis. Copper is an essential cofactor for all organisms, but if concentrations of it exceeds a threshold maintained by dynamic balance mechanisms, it will become toxic. A new form of copper-induced cell death was proposed in a study recently published in Science by Tsvetkov et al. [7]. The study found that the accumulation of copper in cells triggered the aggregation of mitochondrial lipoylated proteins and the instability of Fe-S cluster proteins, leading to a unique type of cell death called cuproptosis [8]. However, the specific mechanism of in EC is not completely clear.

In recent years, the subcellular localization of RNAs has attracted attention as a common phenomenon that affects numerous cellular processes. This was also obvious for the large and relatively novel class of long noncoding RNA (lncRNAs)[9]. LncRNAs are RNA molecules with a transcript length of more than 200 nt and lack the ability to encode proteins. They regulate gene expression by interacting with protein, RNA and DNA. Their functions are closely related to their subcellular localization and play different roles in the nucleus and cytoplasm. It has been proved that the abnormalities of lncRNAs can inhibit or cause cancer and play an important role in the development of tumor[10]. Tumor mutation burden (TMB) is a new biomarker for predicting the effect of immunotherapy. TMB referred to the total number of somatic gene coding errors, base substitutions, and gene insertions or deletions detected across per million bases[11]. It is generally believed that the higher the TMB, the more new antigens will be produced, and the immunogenicity of the body will increase, which makes tumor-specific T cells recognize the new antigens and eventually produce immune response[12]. Immune checkpoint inhibitors (ICIS) have provided more options for the treatment of many cancers. At present, TMB has been identified as a biomarker of melanoma ICIS and has been deeply explored in lung cancer[13]. TMB has a certain value in guiding the immunotherapy of EC. Over recent years, with the development of sequencing technique, the mutation data of different tumors can be obtained from public databases, such as The Cancer Genome Atlas (TCGA) database. A large number of these data resources have been used to determine the relationship between cancer and prognosis and immune microenvironment. However, at present, researchers have not paid attention to the prognosis, immune-related function and potential drug screening of cuproptosis-related lncRNA in EC. The purpose of our study is to determine the prognosis, immune-related function and potential drug screening of cuproptosis-related lncRNA in EC, and to provide new ideas for the treatment of EC.

4. Methods

4.1. Acquisition of transcriptome data, somatic mutation profiles and clinical data

Firstly, we downloaded the gene expression information and transcriptome data of 577 EC tissues from TCGA database (https://portal.gdc.cancer.gov/), including 23 normal tissues and 554 EC tissues. Secondly, somatic mutation profiles of all tumor samples in the "Masked Somatic Mutation" category were obtained from TCGA database, and further mutation analysis was carried out. Then, R software "maftools" package was used to analyze various mutations, and 15 genes with the highest mutation frequency were selected for visualization. Thirdly, we gained the clinical information of 548 patients from TCGA database, including age at the time of diagnosis, sex, tumor grade, tumor stage, survival time and survival status.

4.2. Extraction of cuproptosis gene expression and cuproptosis-related lncRNA expression

First of all, we sort out the transcriptome data through Perl script (version: 5.30.0) (https://www.perl.org/) and divided the data into mRNA and lncRNA groups. Then the R software "limma" package was used to extract the expression of cuproptosis-related genes in EC. The correlation between cuproptosis-related genes and lncRNA was obtained by co-expression analysis, and the correlation results were visualized. Finally, the expression of cuproptosis-related lncRNA was extracted by R software "limma" package.

4.3. Construction of lncRNA prognostic model related to cuproptosis

We first combined the expression of cuproptosis-related lncRNA with the survival time and survival status of the patients through the R software "limma" package. Then the data were randomly divided into two groups: train group and test group by R software. Univariate Cox analysis was performed in train group, and the expression of lncRNA related to prognosis was obtained. We extracted the expression of univariate significant lncRNA for Lasso regression analysis, constructed Lasso regression model and cross-verified, screened 12 lncRNAs, and visualized the correlation between 12-lncRNAs and cuproptosis-related genes. Then the 12 lncRNAs were used to construct the Cox model, and the table containing the names of lncRNAs and their regression coefficient (β) and the optimal model formula are output.The formula was as follows: risk score = expression of lncRNA1 * β1lncRNA1 + expression of lncRNA2 * β2lncRNA2 + … + expression of lncRNAn * βnlncRNAn. Through the formula, we could get the risk score of patients in the train group. According to the median of the score, all samples were divided into high- and low-risk groups. Finally, we used principal component analysis (PCA), risk curve and ROC curve to predict the accuracy of the model. Survival analysis, progression free survival analysis (PFS), independent prognostic analysis, clinical grouping model verification and nomogram to evaluate the prognostic value of the model.

4.4. Differentially expressed genes (DEGs) in two risk groups and functional analysis

All patients were divided into high-risk group and low-risk group, and the DEGs between the high-risk group and the low-risk group were screened out according to |Log FC|>1 and P<0.05 by using the software "limma" package. KEGG and GO analysis were used to analyze the important functional biological pathway of DEGs with false discovery rate (FDR)<0.05.

4.5. Calculation, difference analysis and survival analysis of TMB

We calculated the TMB of each patient by Perl script (version 5.30.0)

with the formula: TMB = (total number of variants) / (the whole length of exons), and then divided all patients into high-TMB group and low-TMB group according to the median TMB. Kaplan-Meier survival analysis was carried out in the high-and low-TMB groups, and TMB was combined with the model we built for survival analysis. Finally, the difference of TMB between high- and low-risk groups was analyzed by R software "limma" and "ggpubr" packages.

4.6. Analysis of immune-related functions and screening of potential drugs for EC

We made ssgsea analysis of patients in two risk groups by R software, and obtained the immune functions with differences in high- and low-risk groups, and then displayed the immune functions with significant differences on the heat map by R software "pheatmap" package. Finally, the high- and low-risk groups were analyzed by R software, and the drugs with significant differences between the two groups were predicted and screened out.

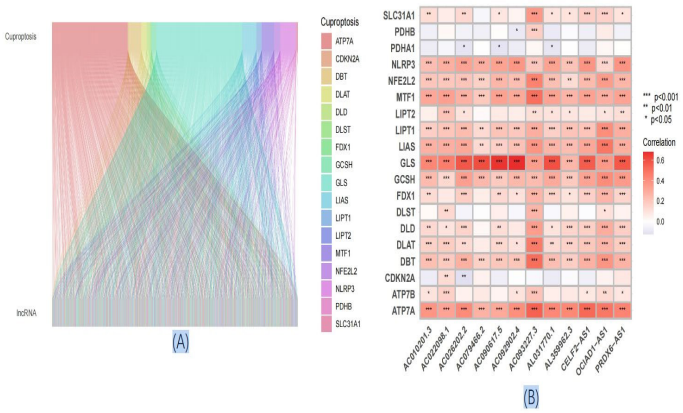
4.7. Statistical analysis

All statistical analyses were carried out with R software (version 4.1.2). Survival analysis was performed by Kaplan-Meier and Log-rank test.The cut-off values of continuous variables, such as age of diagnosis, TMB and risk scores, were determined by the median. Statistical significance was set by $P < 0.05$.

5. Results

5.1. Construction of lncRNA prognostic model related to cuproptosis and prognostic value analysis

We obtained gene expression information, transcriptome data and clinical data of 577 cases of EC from TCGA database. The expression of genes related to cuproptosis in each sample was extracted from the gene expression information, and mRNA and lncRNA genes were distinguished from transcriptome data. Through co-expression analysis, we found lncRNA related to cuproptosis and visualized the correlation results with Sankey diagram (Figure 1A).

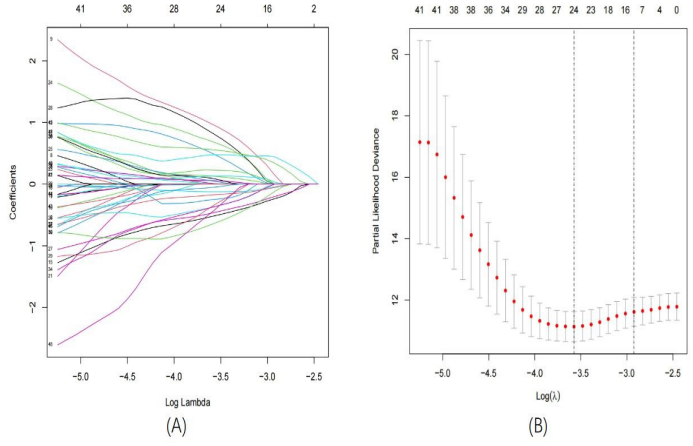


The expression of lncRNA associated to cuproptosis was extracted from all samples, and then combined with the survival time and survival status of patients. We randomly divided the data into two groups: train-group and test-group. Through clinical statistical analysis of the groups, as shown in Table 1, there was no difference in clinical traits between the two groups, which indicated that there was no deviation of clinical traits in sample grouping (P>0.05).

Table 1: Clinical statistical analysis of the two groups.

Covariates	Type	Total	Test	Train	P value
Age	<=65	306(56.35%)	154(56.83%)	152(55.88%)	0.815
Age	>65	235(43.28%)	115(42.44%)	120(44.12%)	
Age	unknow	2(0.37%)	2(0.74%)	0(0%)	
Grade	G1	99(18.23%)	52(19.19%)	47(17.28%)	0.2858
Grade	G2	121(22.28%)	66(24.35%)	55(20.22%)	
Grade	G3	312(57.46%)	146(53.87%)	166(61.03%)	
Grade	unknow	11(2.03%)	7(2.58%)	4(1.47%)	
Stage	Stage I	339(62.43%)	170(62.73%)	169(62.13%)	0.3169
Stage	Stage II	52(9.58%)	25(9.23%)	27(9.93%)	
Stage	Stage III	123(22.65%)	66(24.35%)	57(20.96%)	
Stage	Stage IV	29(5.34%)	10(3.69%)	19(6.99%)	

Subsequently, we gained the significant lncRNA expression of single gene by univariate Cox analysis of train-group data, and then constructed the Lasso regression model by Lasso regression analysis and cross-validation (Supplementary Figure 1).



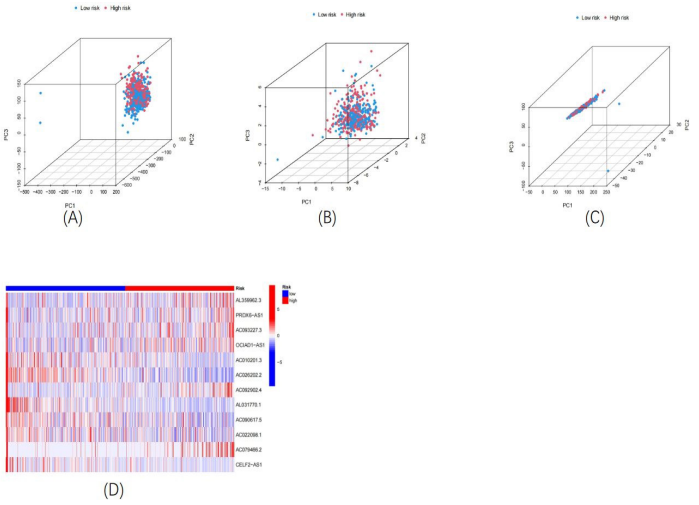
Journal of Bioscience & Bioengineering

Therefore, we screened 12 cuproptosis-related lncRNAs, including AC010201.3, AC022098.1,AC026202.2,AC079466.2,AC090617.5,AC092902.4,AC093227.3,AL031770.1,AL359962.3,CELF2−AS1,OCIAD1−AS1 and PRDX6−AS1, and their correlation with cuproptosis-related genes was shown in Figure 1B. The Cox model of 12-lncRNAs was constructed, and the table (Table 2) containing the name of lncRNAs and their regression coefficient (β) and the optimal model formula were output. As shown in Table 2, each lncRNA has its own regression coefficient (β).

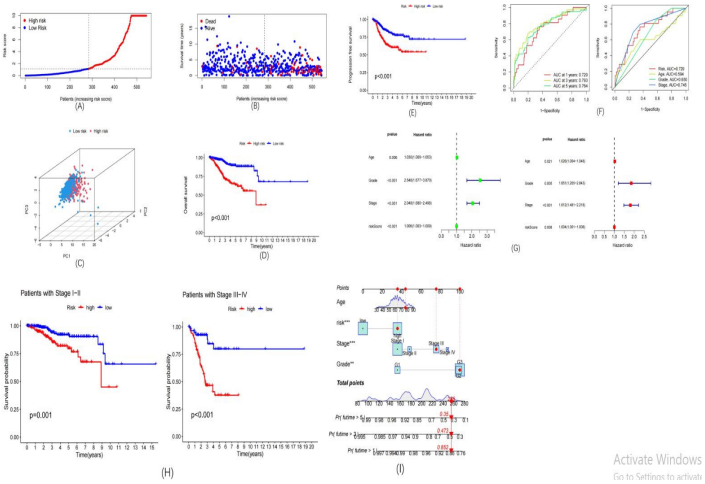
Table 2: 12-lncRNAs and their regression coefficient (β).

Name	coefficient (β)
AL359962.3	2.5005633463881
PRDX6-AS1	0.833183215899793
AC093227.3	1.74654775642408
OCIAD1-AS1	0.487167219388639
AC010201.3	-2.26414747723346
AC026202.2	-1.40389130466005
AC092902.4	2.32561473714713
AL031770.1	-2.19978899551435
AC090617.5	-0.702837816783383
AC022098.1	-1.48286472782715
AC079466.2	0.824285962524997
CELF2-AS1	-3.58304846070853

The risk score can be calculated according to the following criteria:Riskscore = AL359962.3*(2.5005633463881) + PRDX6-AS1*(0.833183215899793) +AC093227.3*(1.74654775642408) + OCIAD1-AS1*(0.487167219388639) + AC010201.3*(-2.26414747723346) + AC026202.2*(-1.40389130466005) + AC092902.4*(2.32561473714713) + AL031770.1*(-2.19978899551435) + AC090617.5*(-0.702837816783383) + AC022098.1*(-1.48286472782715) + AC079466.2*(0.824285962524997) + CELF2-AS1*(-3.58304846070853). Through the constructed prognosis model, each patient in the train group had his own risk score. The same method was adopted to calculate the risk score of all patients, and the median value of risk score was calculated. All samples were divided into high-risk and low-risk groups (Figure2A). Draw risk curves for all samples. As we expected, with the increase of risk score, the number of deaths also increased (Figure 2B). In addition, we could distinguish which of the screened 12 lncRNAs were high-risk lncRNAs and which were low-risk lncRNAs (Supplementary Figure 2D). In order to verify the accuracy of our model, principal component analysis (PCA) was used to analyze it. We found that patients in the high- and low-risk groups were completely separated in the 12-lncRNAs model, which means that the risk model was well distinguishable for patients (Figure 2C and Supplementary Figure 2A-2C). Drawing the Kaplan-Meier survival curve has helped to show the survival performance more intuitively. The results showed that the survival rate of the high-risk group was lower than that of the low-risk group(P<0.001) (Figure 2D).



In addition, the progression free survival (PFS) in the high-risk group was also lower than that in the low-risk group (P<0.001) (Figure 2E). The ROC curve showed that the prognostic model had good predictability with area under the curve (AUC) was 0.729, and could also predict the 1-, 3- and 5-year survival rates of patients (Figure 2F). Subsequently, we conducted an independent prognostic analysis of the 12-lncRNAs model, and found that our model can be used as an independent prognostic factor independent of other traits (Figure 2G). Furthermore, we also carried out the model verification of clinical grouping to observe whether our model was used in patients of different clinical stages, and it has been proved that the model was indeed suitable for patients of different stages (Figure 2H). Therefore, we made a nomogram to predict the patient's survival (Figure 2I). In this nomogram, we could predict the 1-, 3- and 5-year survival rate of patients by getting a total score according to their age, disease grade, stage and risk score.

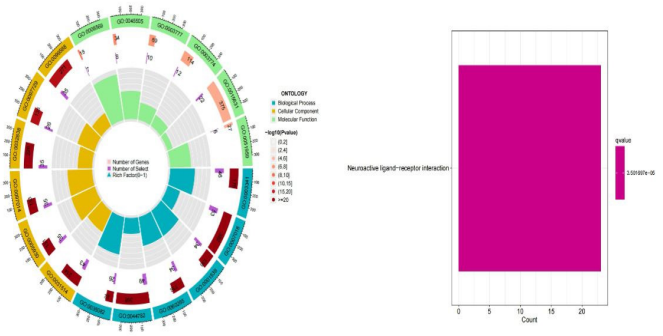


5.2. Differentially expressed genes (DEGs) in high- and low-risk groups and functional analysis

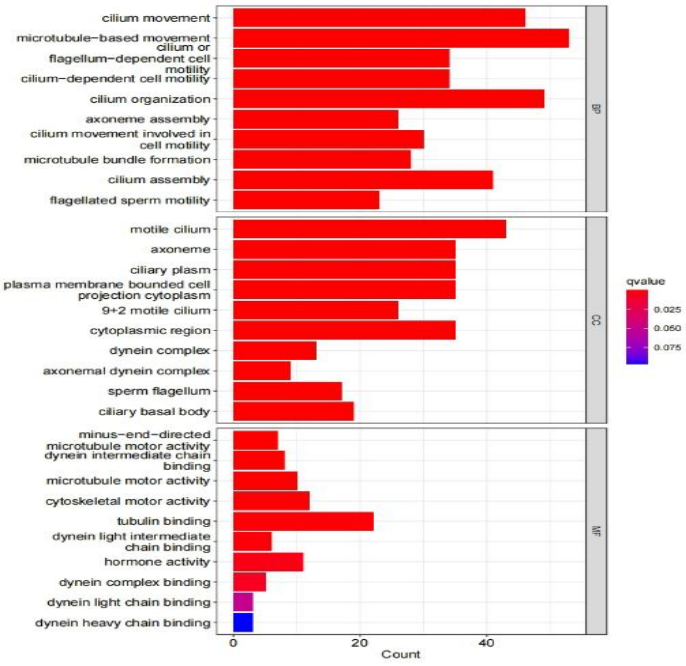
According to |Log FC|>1 and P<0.05, we screened out the DEGs in the high-and low-risk groups. In the functional analysis shown in Figure 3A,3B and Supplementary Figure3, Gene Ontology (GO) analysis found that most DEGs were enriched in microtubule−based movement

Journal of Bioscience & Bioengineering

of biological process (BP) motile cilium of cellular component (CC) and tubulin binding of molecular function (MF). Additionally, according to Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, DGEs were only enriched in Neuroactive ligand−receptor interaction. These have certain significance for our follow-up study of cuproptosis-related lncRNA in EC.

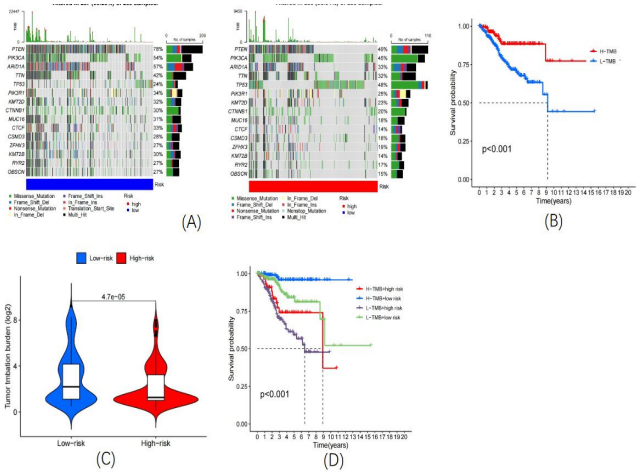


Supplementary Figure3:



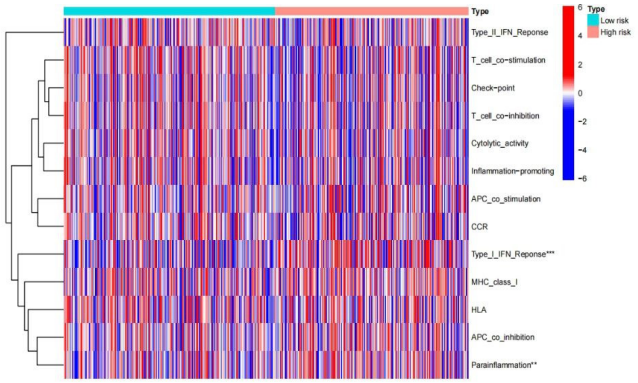
5.3. TMB difference analysis and survival analysis of two risk groups

To understand the potential role of TMB in EC. We obtained the somatic mutation profiles of 519 patients with EC from TCGA database and divided these patients into high- and low-risk groups according to the median risk score. Moreover, the somatic mutation profiles of 519 patients were analyzed and 15 genes with the highest mutation frequency were selected for visualization (Figure 4A). From figure 4A, we could find that there were 269 samples in the low-risk group, of which about 267 (99.26%) had somatic mutations; in the high-risk group, 238 (96.64%) had somatic mutations. In addition, we also found that PTEN gene mutation frequency was the highest, 78% and 49%, respectively, and the overall mutation frequency in the high-risk group was lower than that in the low-risk group. TMB was the total number of somatic gene coding errors, base substitutions, and gene insertions or deletions detected per million bases. We calculated the TMB of each patient and according to the median of TMB, the patients were divided into high-TMB group and low-TMB group. It was found that the survival rate of low-TMB group was lower than that of high-TMB group (P<0.001) (Figure 4B). Then we studied the TMB of patients between the high-and low-risk groups, and we found that there was a significant difference in TMB between the high-and low-risk groups (P=0.000047). Furthermore, the TMB of the low-risk group was higher than that of the high-risk group, which was consistent with our previous conclusion (Figure 4C). Finally, in EC, TMB and 12-lncRNAs seem to have a common impact on the survival outcome of patients, as shown in the Figure 4D, patients with high TMB and low lncRNA expression have the best prognosis.



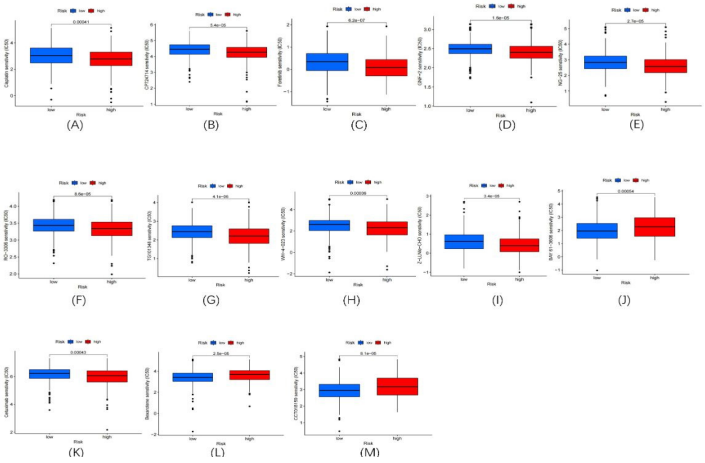
5.4. Analysis of immune-related function

In order to study which immune functions are related to 12-lncRNAs in EC, we analyzed the immune-related functions. We found that there was a significant difference in immune function between Type I IFN response and Parainflammation (PI) in high- and low-risk groups (Figure 5).



5.5. Screening of potential drugs for EC

To explore the possible application of 12-lncRNAs in individualized treatment of EC, we examined the relationship between the risk score and IC50 of drugs commonly used, or unused in EC. As shown in figure 6A-6M, these drugs were Cisplatin, CP724714, Foretinib, GNF-2, NG-25, RO-3306, TG101348, WH-4-023, and Z-LLNle-CHO, Bay 61-3606, Cetuximab,Bexarotene and CCT018159. We discovered that high-risk EC patients seem to be more sensitive to most drugs than low-risk patients, which has a certain reference value for our follow-up drug treatment of EC.



6. Discussion

Mutations in the non-coding genome have now been considered as the main determinants of human cancer [10,14]. Although lncRNA lacks protein-coding sequences, they can be used as important regulators of RNA[10,15]. LncRNA fold into a complex three-dimensional structure that can form specific interactions with proteins. They can interact with RNA or DNA molecules through base pairing to form a functional network composed of DNA, protein and RNA. The function of lncRNA is related to its unique subcellular localization. LncRNA, located in the nucleus, is involved in gene regulation at epigenetic and transcriptional levels, and in post-transcriptional and translation levels in the cytoplasm. LncRNA participates in the regulation of multiple signaling pathways at multiple levels (epigenetic, transcriptional, post-transcriptional and translational) by combining with key components of different signaling pathways, thus promoting the formation of complex regulatory networks in tumor cells. Therefore, lncRNA is widely involved in the proliferation, migration, invasion and drug resistance of cancer cells [10, 16]. Alternative splicing is an important mechanism of genetic diversity, so it can affect the occurrence and development of cancer. It was well known that most eukaryotic genes could be expressed as various alternative splicing variants. Some studies have shown that lncRNA was also involved in the regulation of alternative splicing[17]. Recent studies have revealed the prospects and challenges of targeting lncRNA in the diagnosis and treatment of EC. Compared with normal tissues, the expressions of lncRNA in ECs were up-regulated and down-regulated, and their abnormal expression has been related to tumor grade, FIGO stage, depth of myometrial invasion, lymph node metastasis and patient survival [16]. The view recently put forward by Tsvetkov et al. in science of cuproptosis as a new form of cell death distinct from the former autophagy, apoptotic, necroptosis and ferroptosis. This novel finding of Tsvetkov et al., furthers our understanding of the multiple effects of copper on our human body [18]. In order to explore whether there was cuproptosis in EC and found a more reasonable index to predict the prognosis of EC, we discovered that 12 lncRNAs related to cuproptosis in EC had high accuracy and applicability in predicting the risk of death through Cox regression and Lasso regression analysis.

In recent years, remarkable achievements have been made in the research of lncRNA in EC. More and more lncRNA related to EC have been found. The expression of LncRNA RUNX1-T1 in EC was down-regulated and the proliferation of cancer cells was suppressed by inhibiting the maturation of miR-21 [19]. lncRNA MCTP1-AS1 can inhibit the proliferation, migration, invasion and EMT process of EC cells by targeting miR-650/SMAD7 axis [20]. The LncRNA FOXCUT promoted the process of EC [21]. 12-lncRNAs related to cuproptosis that we have screened out have not been reported yet, and the research on lncRNA in multi-lncRNA signature for EC is still insufficient. Therefore, more research is needed to help explore new and promising targets of EC therapy. Furthermore, we explored the potential functional pathways of DEGs in high- and low-risk groups through KEGG and GO analysis. According to KEGG analysis, we found that DEGs was mainly concentrated in Neuroactive ligand−receptorinteraction. After GO analysis, we got DEGs enriched inmicrotubule−based movement,motile cilium and tubulin binding. At the same time, we first established and verified the prognostic value of multi-lncRNA signature composed of 12-lncRNAs (AC010201.3,AC022098.1, AC026202.2,AC079466.2,AC090617.5,AC092902.4,AC093227.3,AL03 1770.1,AL359962.3,CELF2−AS1,OCIAD1−AS1 and PRDX6−AS1) in EC. We confirmed that patients with high expression of lncRNA related to cuproptosis had lower survival rate and poor prognosis.

A recent study by Joseph M Gozgit etal. showed that PARP7 negatively regulated type I interferon response in cancer cells and inhibited it to trigger of antitumor immunity. In this study, in tumor models, inhibition of PARP7 could restore the signaling responses of type I interferon (IFN) to nucleic acids, and the restored signaling could directly inhibit cell proliferation and activate the immune system, both of which contribute to tumor regression [22]. That is, type I interferon response could inhibit the proliferation of tumor cells and activate the immune system. Parainflammation (PI) is a unique variant of inflammation, characterized by epithelial-autonomous activation of inflammatory response, which is widely prevalent in human cancer, especially in cancers that usually contain p53 mutations[23, 24]. In tumors harboring PI, PI may have the ability to fulfill certain normal macrophage functions.In one study, it was found that PI was closely related to cellular senescence, and as long as P53 was not mutated, it may promote tumor suppression by reinforcing tumor senescence. Once P53 was mutated, PI would become a tumor promoter.Colorectal adenomas was an example. Long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has surprisingly beneficial effects in many types of cancer types, which could prevent or

delay the onset of tumors [24]. In our research, we analyzed the immune-related functions of the screened lncRNA related to cuproptosis, and found that 12-lncRNAs were related to type I interferon response and PI. In EC, there were few studies on type I interferon response and PI, which suggested that we could further explore and provide more choices for the treatment of EC.

Doxorubicin, cisplatin and paclitaxel are currently the most effective chemotherapeutic drugs in the treatment of endometrial carcinoma [25]. About 30% of the ECs belong to the MSI-H/MMRd subgroups. The higher the TMB of these tumors, the more likely they are to be blocked by immune checkpoints [26]. The higher the frequency of gene mutation in tumor cells, the moretumor antigens that can be recognized by the immune system, and the lymphocytes in the body may be mobilized to form tumor infiltrating lymphocytes and inhibit tumor growth. In our study, the prognosis of patients with high TMB was better than that of patients with low TMB. Meanwhile, patients with low expression of cuproptosis-related lncRNA had higher frequency of gene mutation and better prognosis.Immunotherapy has been an available option for a variety of human cancers, the most obvious being melanoma, nonsmall cell lung cancer and kidney malignant tumors. Anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) has made great progress in the treatment of human recurrent / metastatic cancer [27]. In recent years, more and more EC treatment schemes have been proposed step by step. In our study, we screened 13 drugs(Bay 61-3606, Bexarotene, CCT018159, Cetuximab, Cisplatin, CP724714, Foretinib, GNF-2, NG-25, RO-3306, TG101348, WH-4-023, Z-LLNle-CHO) through 12-lncRNAs. We found that most patients with high expression of 12-lncRNAs were more sensitive to drugs. Cetuximab is a recombinant monoclonal lgG1 antibody and epidermal growth factor receptor (EGFR) inhibitor and Cetuximab is approved as the first-line drug in combination with chemotherapy or as a single drug for the treatment of chemotherapy failure or intolerance in patients with RAS wild-type metastatic colorectal cancer expressing EGFR [28]. CP724714 is a ErbB2 inhibitor. A study found that LASP-1 and ErbB2 interact with each other in ovarian cancer. Overexpression of LASP-1 can lead to migration, invasion and proliferation of ovarian cancer cells, and CP724714 can inhibit this effect [29]. Recently, ABL kinase inhibitors including imatinib,nilotinib,dasatinib and bosutinib have been proved to be an interesting therapeutic target in oncology. Dasatinib has been found to be relatively well tolerated in patients with metastatic solid tumors, including gastrointestinal stromal tumor (GIST), melanoma and multiple sarcomas. Bosutinib was found to be well tolerated in patients with advanced solid tumors, including colorectal, pancreatic and ovarian cancer, resulting in one partial response (breast cancer) and one unconfirmed complete response (pancreaticcancer) [30]. NG-25 is a transforming growth factor-β activated kinase 1 (TAK1) inhibitor. TAK1 played a key role in cell survival and inhibition of apoptosis, and inhibition of this kinase could provide a means of inducing cancer cell death, which has been demonstrated in multiple types, including colorectal cancer, lung cancer, and certain blood cancers [31]. RO-3306 is a Cyclin-Dependent kinases (CDKs) inhibitor and Tumor microenvironment has been a hot topic in current research. There are some factors that contribute to cancer progression and inhibit anti-tumor responses in tumor microenvironment. Targeting these tumor-promoting factors in the tumor microenvironment has been considered as an effective immunotherapy for cancer therapy. CDKs are considered as a novel target for cancer therapy. The development and use of CDK-inhibitors have achieved encouraging results in the treatment of breast cancer, and selective blocking of CDK1 alone or in combination with other therapeutic drugs have related to effective anti-cancer effects, so CDK1 may be considered as the best CDK target for breast cancer treatment [32].

TG101348is a JAK-2 inhibitor. It has been studied that 1,4-benzothiazine derivatives AR13 and AR15 played a better antiproliferative effect in DMH-induced colorectal cancer by blocking COX-2/JAK-2/STAT-3 signal transduction pathway [33]. WH-4-023is an inhibitor of Src. Harold Varmus and Mike Bishop identified the first cancer-causing oncogene called Src in 1976. Later experiments and clinical evidence showed that Src kinase played an important role in promoting tumor growth and progression, and its activity was related to the poor survival of patients. Thus, several Src inhibitors have been developed and approved by FDA for the treatment of cancer patients [34]. GSI-I (Z-LLNle-CHO) inhibits γ-secretase and proteosome to trigger B precursor acute lymphoblastic leukemia cell death [35]. Spleen tyrosine kinase (Syk) inhibitor Bay 61-3606 could down-regulate the expression of myeloid cell leukemia sequence-1 (Mcl-1) in breast cancer cells and made cancer cells sensitive to TNF-Related Apoptosis-Inducing Ligand (TRAIL)-mediated apoptosis [36]. Bexarotene has shown inhibitory effect on lung and breast tumors in preclinical models and clinical trials [37]. 3,4-diaryl pyrazole resorcinol HSP90 inhibitor (CCT018159) could cause G(1) arrest and induced cell apoptosis. CCT018159 also inhibited the functions of tumor cells and key endothelial associated with invasion and angiogenesis [38]. In our study, 13 drugs selected have not yet been used in EC. These drugs provide us with new ideas for the treatment of EC. We hope that through our research, we can provide more treatment options for EC.

7. Conclusions

Our team was the first to investigate the role of cuproptosis-related lncRNA in endometrial cancer based on large-scale mutation data and clinical data from a public database.In the present findings, we innovatively expounded that lncRNA related to cuproptosis was associated with the survival of EC. In addition, we constructed and verified the prognostic model of cuproptosis-related lncRNA, which can predict the overall survival of EC. Through this model, we analyzed the immune-related function of 12-lncRNAs in EC and screened out 13 potential therapeutic drugs for EC. Our study has a certain value for the proposal of novel therapeutic targets for EC.

8. Funding

This research was funded by Fudan University Shanghai Cancer Center, Shanghai, China, grant number YJS201930 and the National Nature Science Foundation of China (82102718) for Haoran Li.

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