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Prognostic model of melanoma patients based on autophagy Long non-coding ribonucleic acids.

Autophagy-Related lncRNA in melanoma.

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Abstract

BACKGROUND

Melanomas are melanocyte malignant tumors that can occur in different body parts or tissues such as skin, mucous membrane, eye uveum, and pia meninges. Long non-coding ribonucleic acids (lncRNAs) are becoming key factors in the occurrence and development of many malignant tumors, and are involved in the prognosis of some patients. Identifying the autophagy-related lncRNAs of melanoma is crucial for the diagnosis, treatment and prognosis of melanoma patients.

AIM

Identify the autophagy lncRNAs related to the prognosis of melanoma, and establish a risk model for predicting survival and prognosis.

METHODS

In this research, we correlated autophagy-associated lncRNAs expression with melanoma patients' survival. We obtained a prognostic model and studied autophagy response characteristics in different populations. We retrieved transcriptome expression profiles and clinical information of 470 melanoma patients from the The Cancer Genome Atlas (TCGA) database. Then, we used the Human Autophagy Database website for autophagy-related genes. Using the R software, coexpression analysis of lncRNA and autophagy-related genes was conducted to obtain autophagy-related lncRNAs and their expression levels. We also performed univariate and multivariate Cox proportional risk analyses on the obtained datasets, to systematically evaluate the autophagy-related lncRNAs prognostic value in melanoma. Fifteen autophagy-related lncRNAs were identified and a melanoma autophagy prognostic model was established. The Kaplan-Meier, univariate and multivariate Cox regression analyses were used to calculate risk scores. Based on the risk scores, melanoma patients were randomly divided into high- and low-risk groups. A Receiver Operation Characteristic (ROC) curve analysis, dependent on time, was selected to assess the melanoma

prognostic model's accuracy. At the same time, we also downloaded the melanoma data sets GSE65904, GSE19234, and GSE78220 from the GENE EXPRESSION OMNIBUS (GEO) database for model verification. Finally, we performed Gene Set Enrichment Analysis (GSEA) functional annotation that showed that the low and the high-risk groups had different enriched pathways.

RESULTS

The co-expression network for autophagy-related genes was constructed using R, and 936 lncRNAs related to autophagy were identified. Then, 52 autophagy-related lncRNAs were significantly associated with TCGA melanoma patients' survival by univariate Cox proportional risk analysis ($p < 0.01$). Further, the 52 autophagy lncRNAs mentioned above were analyzed by multivariate Cox analysis with the R software. Fifteen lncRNAs were selected: LINC01943, AC090948.3, USP30-AS1, AC068282.1, AC004687.1, AL133371.2, AC242842.1, PCED1B-AS1, HLA-DQB1-AS1, AC011374.2, LINC00324, AC018553.1, LINC00520, DBH-AS1 and ITGB2-AS1. The p-values in all survival analyses using these 15 lncRNAs were < 0.05 . Use these lncRNAs to build a risk model based on the risk score. Negative correlations were observed between risk scores and overall survival rate in melanoma patients over time. Additionally, the melanoma risk curves and scatter plot analyses showed that the death number increased along with the risk score. Overall, we identified and established a new prognostic risk model for melanoma using 15 autophagy-related lncRNAs. The risk model constructed with these lncRNAs can help and guide melanoma patients prognosis predictions and individualized treatments in the future.

CONCLUSION

Overall, these 15 autophagy-related lncRNAs risk models can have important melanoma prognostic value and may provide autophagy-related clinical targets for melanoma treatment.

Key Words: Melanoma, Long non-coding ribonucleic acids (lncRNAs), Autophagy, Prognosis, The Cancer Genome Atlas (TCGA), Bioinformatics.

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Core Tip: Long-chain non-coding RNA (lncRNA) is becoming a key factor in the development of many malignant tumors and is involved in the prognosis of some patients. The expression of autophagy associated lncRNAs was associated with survival in melanoma patients. We obtained 15 autophagy-related lncRNAs and established a melanoma prognosis model, which can predict the prognosis of melanoma patients and is more accurate than TNM stage, age, gender and other clinical indicators, and may provide autophagy-related clinical targets for the treatment of melanoma.

INTRODUCTION

Melanomas are melanocyte malignant tumors that can occur in different body parts or tissues such as skin, mucous membrane, eye uveum, and pia meninges. While the incidence of many tumors is declining, melanoma continues to increase^[1]. The global prevalence of melanoma is increasing about 3 to 7% per year^[2]. Although many melanoma patients have localized tumors at diagnosis that were completely removed with surgery, many patients present signs of metastasis^[3]. Early melanoma has a good prognosis, but advanced melanoma patients have a very poor prognosis, with a 5-10% survival rate, even with treatment^[4]. Autophagy, originally considered a lysosomal-dependent degradation of cytoplasmic components in response to starvation, has been shown to affect multiple homeostasis aspects and to constitute a prevention barrier to malignant transformations^[5]. Therefore, the combination of autophagy-related factors and pathological classification for risk stratification in melanoma patients can be crucial to prognosis and treatment response predictions.

Long non-coding RNAs are transcribed RNAs with more than 200 nucleotides that are not translated into proteins [6]. Many studies have shown that noncoding RNAs can be associated with tumor pathogenesis by epigenetic regulation, as well as transcriptional and/or post-transcriptional processes. Moreover, lncRNAs can be used as sensitive and specific cancer biomarkers [7-10]. Previous studies have shown that melanoma pathogenesis was associated with different lncRNAs, *in vitro* and *in vivo*, and that some of them can be potential melanoma therapy targets, such as UCA1, DSCAM-AS1, and miR155HG [11-13]. However, the lncRNAs involved in autophagy and their prognostic values were not previously investigated, and many mechanisms remain unclear.

Therefore, we retrieved human clinical melanoma datasets from the The Cancer Genome Atlas (TCGA) database and screened and analyzed genes associated with melanoma prognosis. Finally, 15 autophagy-related lncRNAs were identified as melanoma prognosis biomarkers. Compared to other clinical indicators, these lncRNAs had higher accuracy to predict melanoma patients' survival.

MATERIALS AND METHODS

Patient characteristics and data processing

The data of 471 melanoma patients were retrieved from the TCGA database (<https://cancergenome.nih.gov/>). In addition, the GSE65904, GSE19234 and GSE78220 data sets were downloaded from the GEO database, including the expression data and clinical information of a total of 265 melanoma patients (<https://www.ncbi.nlm.nih.gov/geo/>). In this study, the lncRNAs expression data in the TCGA database included complete clinical and follow-up data of 349 patients, which were finally used for analyses. Patients' clinical characteristics are detailed in Table 1. This study followed the TCGA published guidelines, and since the data used here were from the published TCGA database, Institutional Review Board (IRB) approval is not required.

Autophagy-related genes acquisition and co-expression networks establishment

The Human Autophagy Database (HADB) was used to identify autophagy-related genes. Then, the R software was used to analyze the association of autophagy-related genes and lncRNAs (condition were: Correlation Coefficient > 0.3; p-value filter < 0.001), and a co-expression network was constructed. Finally, 936 melanoma autophagy-related lncRNAs were identified, and their expression levels were obtained.

Autophagy lncRNAs signaling related to melanoma prognosis

The univariate proportional risk, Kaplan-Meier survival, and multivariate risk analyses were conducted using the R software to calculate patients' risk scores and to identify if these autophagy-related lncRNAs were involved in the melanoma prognosis. The risk score was calculated using the formula: Risk score = $\text{expr}(\text{lncRNA1}) \times \text{coef}(\text{lncRNA1}) + \text{expr}(\text{lncRNA2}) \times \text{coef}(\text{lncRNA2}) + \dots + \text{expr}(\text{lncRNA}_n) \times \text{coef}(\text{lncRNA}_n)$. Melanoma patients were divided into high- and low-risk groups, based on the median risk score. Finally, three data sets from the GEO database (GSE65904, GSE19234 and GSE78220) for verification analysis.

Multi-indicator ROC curve and independent prognostic analysis

Univariate and multivariate regression analyses were used to systematically access the relations between prognosis, clinicopathological factors, and risk scores in melanoma patients. To evaluate and verify the prognostic model prediction accuracy, we conducted ROC analysis on the data from the TCGA database and the GSE78220 data set from the GEO database, and drew the ROC curve.

Co-expression network and Gene Set Enrichment Analysis (GSEA)

A co-expression network with 15 prognostic autophagy-related genes was constructed using the R software (Version 4.0.4). The mulberries were mapped and the network was visualized using Cytoscape. Then, survival curves were drawn for these 15 lncRNAs, and risk survival and risk curves were drawn. Then, GSEA was employed for functional annotation. The GSEA focused not only on high-score genes but also on a range of genes related to biological processes that are associated with cancer pathogenesis, including stress response, transcription, and metabolic pathways. A $p < 0.05$ was considered statistically significant [14].

RESULTS

Identification of autophagy-related lncRNAs and a melanoma prognostic model establishment

The co-expression network for autophagy-related genes was constructed using R, and 936 lncRNAs related to autophagy were identified. Then, 52 autophagy-related lncRNAs were significantly associated with TCGA melanoma patients' survival by univariate Cox proportional risk analysis ($p < 0.01$). Among the 52 autophagy-related lncRNAs, 4 were at high risk (Table 2). Further, the 52 autophagy lncRNAs mentioned above were analyzed by multivariate Cox analysis with the R software. Fifteen lncRNAs were selected: LINC01943, AC090948.3, USP30-AS1, AC068282.1, AC004687.1, AL133371.2, AC242842.1, PCED1B-AS1, HLA-DQB1-AS1, AC011374.2, LINC00324, AC018553.1, LINC00520, DBH-AS1 and ITGB2-AS1 (Table 3). They were subsequently used to construct a melanoma prognostic risk model (Figure 1A-B). Then, we assigned the enrolled melanoma patients into two groups based on their median risk scores. The p-values in all survival analyses using these 15 lncRNAs were < 0.05 (Figure 2). To investigate the survival rates in these groups, other survival analyses were performed. Negative correlations were observed between risk scores and overall survival rate in melanoma patients over time (Figures 3A). Additionally, the melanoma risk curves and scatter plot analyses showed that the death number increased along with the risk score. Therefore, this demonstrated that the melanoma patients' mortality was related to the risk score (Figure 3B-D). The heat map produced with these 15 autophagy-related lncRNAs showed that LINC00520 and AC018553.1 were highly expressed in the high-risk group. High expressions of others lncRNAs were observed in the low-risk score patients. In order to verify the accuracy and stability of the model, we decided to use the GSE65904, GSE19234 and GSE78220 data sets from the GEO database to verify, and conduct survival analysis, risk curve, scatter plot and heat map analysis, and the results are basically consistent with the above analysis (Figure 6-9). Overall, we screened 15

pairs of melanoma lncRNAs with prognostic significance, paving the way for the subsequent melanoma prognostic model establishment.

Evaluation of an independent prognostic risk model for melanoma patients

The above analyses identified 15 lncRNAs and established a prognostic risk model for the was. Next, multivariate and univariate Cox regression analyses were employed to confirm if this model could be used in melanoma prognosis and other independent factors. Results showed that the hazard ratio (HR) was 1.912 in the univariate analysis and 1.715 in the multivariate. Additionally, the risk score 95% confidence interval was 1.643-2.226 ($p < 0.001$) and 1.467- 2.005 ($p < 0.001$) in the univariate and multivariate analyses, respectively (Figure 4A-B). These results suggested that in our model the most important prognostic factors for melanoma are not age, gender, or TMN staging, but the 15-lncRNAs. To verify the risk model sensitivity and specificity, ROC curves of risk scores and other clinical indicators were plotted. The area under the risk score curve (AUC) was 0.712, exceeding the other clinical factors AUC of (Figure 4D). In addition, we also verified the above analysis in three datasets of GEO database, and the analysis results are consistent with those of TCGA database (Figure 10). These results suggested that the risk model was more accurate than other clinicopathological factors in predicting melanoma patients' prognosis.

Different autophagy states in melanoma patients

The GSEA software (version 4.1.0) was used for functional annotation. The differentially expressed genes of the high-risk group were mainly enriched in glyoxylate and dicarboxylate metabolism, while in the low-risk group pathways such as antigen processing and presentation, toll-like receptor signaling, cytokine production positive regulation were enriched (Figure 5).

DISCUSSION

As an aggressive tumor, melanoma has a poor prognosis and increasing incidence in the metastatic phase^[15]. The main high mortality rate reason is late diagnosis ^[16].

Studies have found that the distant metastases melanoma patients' survival rate was only 5-10% [17]. Therefore, melanoma early detection and diagnosis are crucial to improving the survival rate. At present, TNM staging is commonly used to treat and evaluate the melanoma prognosis. However, some studies have found that TNM staging methods have differences in overall survival rates^[18]. Increasing studies have shown that tumor TNM staging also has clinical limitations^[19, 20]. Therefore, new melanoma diagnosis and prognosis methods are required to improve melanoma patients' prognosis and survival rate. Autophagy's promotive and suppressive effects on the development of tumors were observed by many previous studies ^[21, 22]. In other words, autophagy is a dual process regarding tumors. For example, Mgrditchian *et al* reported that autophagy can recruit natural killer cell infiltration into tumor tissues, and subsequently reduce the melanoma growth *in vivo* ^[23]. At the same time, Luan *et al*^[24] showed that POL can downregulate miR1290, leading to BECN1 upregulation and enhanced autophagy, thereby reducing the survival of melanoma cells. However, Xiao *et al* showed that beclin-1 expression and LC3-II/I ratio were significantly enhanced by miR-24-1-5p. Meanwhile, they also observed the miR-24-1-5p promotive effect on autophagy and subsequently inhibitory function in melanoma cells' proliferation ^[25]. The studies listed above showed both positive and negative effects of autophagy on tumor development, and that autophagy plays a crucial role in this process.

Additionally, the lncRNA roles in the pathogenesis of different tumors were identified by other researchers, including breast cancer, lung cancer, hepatocellular carcinoma ^[26-28]. In this study, we analyzed and identified 15 lncRNAs that can be related to melanoma survival and prognosis, and established a risk model for melanoma independent prognostic factors. We consulted many previous studies and found that only LINC00520 and DBH-AS1 have been linked to melanoma. USP30-AS1, PCED1B-AS1, LINC00324, ITGB2-AS1, LINC00520, and DBH-AS1 have also been reported in other tumors. The remaining lncRNAs (LINC01943, AC090948.3, AC068282.1, AC004687.1, AL133371.2, AC242842.1, HLA-DQB1-AS1, AC011374.2, and AC018553.1) have not yet been reported. LINC00520 can promote melanoma's

proliferative and metastatic capabilities by competitively targeting miR-125b-5p and acting on the miR-125b-5p/eIF5A2 axis *in vivo* [29]. Also, LINC00520 can be involved in the progressive processes of many tumors. For example, Wenkang Luan *et al* pointed out that through MiR-3175 suppression, LINC00520 was involved in lung cancer's progression^[30]. Xi-Han Jin *et al* found that LINC00520 can act as a miR-577 competitive suppressor to enhance HSP27 expression, leading to colorectal cancer progression [31]. Besides, LINC00520 can promote thyroid papillary carcinoma, nasopharyngeal carcinoma, breast cancer, and non-small cell lung cancer progression, being a poor prognostic factor for these tumors^[32-36]. X.-X. CHEN *et al* found that DBH-AS1 can enhance melanoma cells' glycolytic activity, thereby blocking the miR-223-3p/EGFR/AKT axis^[37]. Crucial lncRNA DBH-AS1 roles were also observed in osteosarcoma, diffuse large b-cell lymphoma, liver cancer, and non-small cell lung cancer [38-42]. In our analyses, both DBH-AS1 and LINC00520 were high-risk autophagy-related lncRNAs. Their elevated expression in melanoma patients indicated a poor prognosis. Through miR-229-3p isolation and subsequently enhancing PTP4A1^[43], USP30-AS1 expressions can promote cervical cancer malignant progression. The lncRNA, pCED1B-AS1, can activate glioma proliferation and limit apoptosis, working with the miR-194-5p/ pCED1B axis^[44]. pCED1B-AS1 can also induce hepatocellular carcinoma immunosuppression through PD-1 and PD-L1 regulation *via* the Sponge HSA miR-1945p^[45]. Other studies have shown that lncRNA pCED1B-AS1 can also promote clear cell renal carcinoma and pancreatic ductal adenocarcinoma progression [46, 47]. Important roles of lncRNA LINC00324 and A ITGB2-AS1 have been observed during different tumors progressions. For example, osteosarcoma proliferative and invasive capabilities were promoted by LINC00324 through WDR66 regulation. Also, LINC00324 promotive effects on papillary thyroid carcinoma progression were found, due to its regulatory effect on Notch-related pathways [48, 49]. The lncRNA, ITGB2-AS1, can upregulate ITGB2 and promote breast cancer cells migration and invasion. Besides, ITGB2-AS1 can also promote pancreatic ductal adenocarcinoma growth and metastasis, acting on the miR-4319/RAF1 axis [50, 51].

Additionally, the mechanism of the remaining 9 lncRNAs identified by our study (LINC01943, AC090948.3, AC068282.1, AC004687.1, AL133371.2, AC242842.1, HLA-DQB1-AS1, AC011374.2, AC018553.1) has not been yet reported, and there are still great research opportunities. Five of them, such as PCED1B-AS1, ITGB2-AS1, AC018553.1, LINC00520, and DBH-AS1, were risk-related lncRNAs, and their increased expression levels suggested a poor prognosis. The remaining 10 lncRNAs (LINC01943, AC090948.3, USP30-AS1, AC068282.1, AC004687.1, AL133371.2, AC242842.1, HLA-DQB1-AS1, AC011374.2, LINC00324) were protective lncRNAs, and their elevated expression levels in melanoma patients predicted a good prognosis. The survival analysis p-value (2.287×10^{-14}) suggested a significant difference between the survival rate of the high- and low-risk score patients. Meanwhile, we also observed negative correlations between the risk scores and overall survival rate in melanoma patients. Finally, we constructed the ROC curve, and the AUC value was 0.712, higher than the AUC of all clinicopathological indicators analyzed. Not only that, we also downloaded 265 melanoma samples from three datasets from GEO database to verify the accuracy of this model, and the results are consistent with the previous analysis. These results demonstrated that the prognostic model established by autophagy-related lncRNAs in melanoma patients had higher prognostic accuracy than other clinical indicators. Altogether, results showed model accuracy, and that the risk model established by the 15 autophagy-related lncRNAs could better predict melanoma patients' prognosis and survival.

The GSEA analysis revealed the difference in signaling pathways enrichment between the high- and low-risk melanoma patients. In low-risk populations, the main significant aggregation route were immune ones, such as antigen processing and presentation, toll-like receptor signaling pathway, systemic lupus erythematosus, and autoimmune thyroid disease. The high-risk populations were mainly enriched in the metabolism, such as glyoxylate and dicarboxylate signaling pathways. These results indicated that the immunity improvement might be related to melanoma patients'

prognosis improvement and that a poor prognosis can be associated with glyoxylate and dicarboxylate metabolic pathways.

Recently, increasing studies have explored lncRNAs significance in cell autophagy and their functional effect in tumors attracted researchers' attention. However, the function, mechanisms, and values of these lncRNAs in clinical melanoma prognosis remained unclear. Our current study proposed a new melanoma risk model composed of 15 lncRNAs involved in autophagy that can be helpful for future melanoma treatments and prognosis evaluation. However, our research also has limitations. Although the data and analyses used have been verified for their accuracy in different studies, our study was not verified experimentally. The molecular mechanism of phagocytosis-related lncRNAs has not yet been elucidated, and some lncRNAs have never even been reported in the literature. Therefore, further experimental studies are required to verify our results.

CONCLUSION

Overall, we identified and established a new prognostic risk model for melanoma using 15 autophagy-related lncRNAs: LINC01943, AC090948.3, USP30-AS1, AC068282.1, AC004687.1, AL133371.2, AC242842.1, PCED1B-AS1, HLA-DQB1-AS1, AC011374.2, LINC00324, ITGB2-AS1, AC018553.1, LINC00520, DBH-AS1. The risk model constructed with these lncRNAs can help and guide melanoma patients prognosis predictions and individualized treatments in the future.

ARTICLE HIGHLIGHTS

Research background

At present, melanoma is mainly treated by surgical resection, but many patients have tumor metastasis, and patients with advanced melanoma have a very poor prognosis, so a new method is needed to predict and evaluate the prognosis and survival of patients. Autophagy, originally thought to be a lysosomal dependent cytoplasmic component response to starvation, has been shown to influence multiple dynamic

equilibria and to constitute a barrier against malignant transformation. However, lncRNAs involved in autophagy and their prognostic value have not been studied before, and many mechanisms remain unclear. Therefore, risk stratification of melanoma patients in combination with autophagy-associated lncRNAs and pathological classification is crucial to predict prognosis and treatment response.

Research motivation

The main task of this study is to identify autophagy lncRNAs associated with melanoma prognosis and establish a risk model to predict survival and prognosis. Among the 15 autophagy related lncRNAs analyzed in this study, the mechanism of action of some lncRNAs is still unclear and has not been reported in literature, so further studies are needed to explore the role of these lncRNAs. The solution of this major problem will help us to have a deeper understanding of melanoma and make it possible to completely cure melanoma.

Research objectives

The main goal of this study is to establish a more accurate method for predicting and evaluating the prognosis and survival of melanoma patients. We obtained a prognostic risk model through analysis, and using the risk model to evaluate the prognosis of patients is more accurate than other conventional clinical indicators (such as : Age, gender, TNM staging, etc.), successfully achieved our initial goal. The realization of this goal will help guide clinicians in the treatment of patients with melanoma, and provide new ideas for the formulation of individualized treatments.

Research methods

Firstly, data from Cancer Genome Atlas (TCGA) and GENE EXPRESSION OMNIBUS (GEO) databases were processed, and then R software was used to analyze the correlation between autophagy related genes and lncRNA (correlation coefficient >0.30; P-value filtering <0.001), and a co-expression network was constructed. In order to

evaluate the relationship between autophagy lncRNAs signal transduction and melanoma prognosis, univariate proportional risk, Kaplan-Meier survival and multivariate risk analysis were used. R software was used to calculate the risk score of each patient, and the calculation formula was as follows: Risk score = $\exp R(\text{lncRNA1}) \times \text{COEF}(\text{lncRNA1}) + \exp R(\text{lncRNA2}) \times \text{COEF}(\text{lncRNA2}) + \dots + \exp R(\text{lncRNA}_n) \times \text{COEF}(\text{lncRNA}_n)$. In order to assess the stability of risk models, univariate and multivariate regression analyses and ROC analyses were also used. Finally, GSEA was used for functional annotation and GEO data was used for further validation to ensure the accuracy of the results.

Research results

Recently, increasing studies have explored lncRNAs significance in cell autophagy and their functional effect in tumors attracted researchers' attention. However, the function, mechanisms, and values of these lncRNAs in clinical melanoma prognosis remained unclear. Our current study proposed a new melanoma risk model composed of 15 lncRNAs involved in autophagy that can be helpful for future melanoma treatments and prognosis evaluation. However, our research also has limitations. Although the data and analyses used have been verified for their accuracy in different studies, our study was not verified experimentally. The molecular mechanism of phagocytosis-related lncRNAs has not yet been elucidated, and some lncRNAs have never even been reported in the literature. Therefore, further experimental studies are required to verify our results.

Research conclusions

The new theory of this study is to abandon the traditional evaluation method and find a new and more accurate method to evaluate the prognosis and survival of melanoma patients. Moreover, these lncRNAs in this study are closely related to melanoma, which may be the future Provide a new way to treat melanoma. The new methods of this study include the discovery of new and unreported lncRNAs through a series of

analyses, and are closely related to the prognosis of melanoma patients, providing a new direction for future research on melanoma-related LncRNAs.

Research perspectives

In the future, we can conduct further experimental verification around these 15 LncRNAs to understand the specific mechanism of action and specific role of these 15 LncRNAs in melanoma, and I believe that we will have a deeper understanding of the diseases and treatment of melanoma.

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