• Basic Research •

LncRNA SNHG15 predicts poor prognosis in uveal melanoma and its potential pathways

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Abstract

● **AIM:** To evaluate the role of long noncoding RNA (lncRNA) SNHG15 and its potential pathways in uveal melanoma (UM).

● **METHODS:** The SNHG15 mRNA expression level and corresponding clinicopathological characteristics of 80 patients with UM were obtained from the Cancer Genome Atlas (TCGA) database and further analyzed. The SPSS 24.0 statistical software package was used for statistical analyses. To investigate the potential function of SNHG15 in UM, we conducted in-depth research on Gene Set Enrichment Analysis (GSEA).

● **RESULTS:** The univariate analysis revealed that the age, tumor diameter, pathological type, extrascleral extension, cancer status, and high expression of SNHG15 were statistical risk factors for death from all causes. The multivariate analysis suggested that the mRNA expression level of SNHG15 was an independent risk factor for death from all causes, as was age and pathological type. Kaplan-Meier survival analysis confirmed that UM patients with high SNHG15 expression might have a poor prognosis. In addition, SNHG15 was significantly differentially expressed in the different groups of tumor pathologic stage, metastasis and living status. Besides, the logistic regression analysis indicated that high SNHG15 expression group in UM was significantly associated with cancer status, pathologic stage, metastasis, and living status. Moreover, the GSEA indicated the potential pathways regulated by SNHG15 in UM.

● **CONCLUSION:** Our research suggests that SNHG15 may play a vital role as a potential marker in UM that predicts poor prognosis. Besides, GSEA indicates the underlying signaling pathways enriched differentially in SNHG15 high expression phenotype.

● **KEYWORDS:** SNHG15; uveal melanoma; the Cancer Genome Atlas; pathology; prognosis; Gene Set Enrichment Analysis

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INTRODUCTION

Uveal melanoma (UM), the most common intraocular cancer in adult worldwide[1], is a malignant tumor that originates in melanocytes of the choroid plexus, ciliary body, and iris of the eye. At present, despite definitive radiotherapy or removal of the primary lesion, numerous patients eventually develop metastases and subsequently prognosis is significantly poor[2]. In addition, UM tends to metastasize to liver through hematogenous pathway, a distant site relative to their origins in the eye[3]. There is an incubation period between the enucleation of the primary tumor and the emergence of metastasis, which can range from a few months to several decades[4-5]. Despite the advancement of UM management, there are currently no effective therapy once the metastases occurred[6]. Therefore, close follow-up and further research on the pathogenesis and novel makers exploration of UM are of great significance for accurate diagnosis, appropriate therapy and prognosis prediction.

Long noncoding RNA (lncRNA), is a class of noncoding transcripts with a length of larger than 200 nucleotides[7], which has been involved widely in biological processes of different cancers, including cell cycle, apoptosis, cell differentiation[8-10]. In the development of UM, lncRNA is also reported to play a vital role in cell cycle, cell proliferation, apoptosis, invasion and autophagy[11-13]. For example, silencing of lncRNA PVT1 prevents the development of UM by impairing microRNA-17-3p-dependent MDM2 upregulation[14]. ZNNT1 can suppress

the progression of UM by inducing the expression of crucial autophagy gene[15]. The lncRNA RHPN1-AS1 facilitates the tumorigenesis of UM by influencing cell proliferation and migration[13]. However, the study of vital lncRNAs in UM still remains to be explored.

SNHG15, a novel lncRNA, located on chromosome 7p13[16], is identified to play a key role in many types of human tumors, such as osteosarcoma[17], papillary thyroid carcinoma[18], pancreatic ductal adenocarcinoma[19], colorectal carcinoma[20], hepatocellular carcinoma[21-22], prostate cancer[23], and breast cancer[24]. To our knowledge, the potential impact of SNHG15 on the tumorigenesis of UM seems unclear recently. Thus, the purpose of this study was to evaluate the pivotal role of SNHG15 in the progression of UM. In addition, the relationship between SNHG15 expression and clinicopathologic characteristics in UM was preliminarily demonstrated. To explore the underlying mechanisms of the biological pathways involved in UM, we conducted a research on Gene Set Enrichment Analysis (GSEA).

MATERIALS AND METHODS

Ethical Approval The study protocol was approved by the Ethics Committee of the Eye & ENT Hospital of Fudan University, and all procedures were complied with the principles of the Declaration of Helsinki. All datasets of our present study were downloaded from an open database TCGA, so there was no written informed consent from participants.

RNA-Sequencing Patient Data and Bioinformatics Analysis The RNA-Seq gene expression level and clinicopathological characteristics, including 80 cases, were obtained from the official website of the Cancer Genome Atlas (TCGA) UM project (https://portal.gdc.cancer.gov/). Patients with UM were classified as two groups, based on the median SNHG15 expression level (cutoff value=7.94 FPKM). Finally, 80 patients with UM were retained and their clinicopathological characteristics were further analyzed, including the detailed information of age, gender, tumor diameter, thickness, pathological type, extrascleral extension, cancer status, pathological stage, metastasis, living status, SNHG15 expression.

Gene Set Enrichment Analysis GSEA is a common bioanalysis used to interpret and analyze microarray and other similar data, and to speculate related pathways that can significantly enrich regulatory genes[25]. Through TCGA UM project, we obtained the RNA-Seq gene expression level of 80 UM patients. And the analysis was conducted using GSEA v3.0 software. In this study, according to the association with SNHG15 expression, the ordered gene list was generated firstly by GSEA. Subsequently, GSEA was conducted to clarify statistically significant differences between the two groups with high and low SNHG15 expression. A total of 1000 permutations were performed. The SNHG15 expression level was identified as a phenotype label. The related pathways statistically enriched in each phenotype were selected with the nominal $P<0.05$ and an false discovery rate (FDR) <0.25.

Statistical Analysis The SPSS 24.0 statistical software package (SPSS, Inc., USA) was used for statistical analyses. Both the univariate and multivariate analyses using Cox analysis were performed to demonstrate independent prognostic biomarkers for UM patients. The survival curve was generated by conducting Kaplan-Meier method. To compare the significant differences in overall survival (OS), the log-rank test was conducted. The plot chart was performed to visualize the difference of SNHG15 expression level for diverse variables through Graphpad. The relationship between the SNHG15 expression and clinicopathological characteristics were analyzed using logistic regression. The median value of SNHG15 expression was selected as the cut-off value. $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics The records of 80 primary UM with both RNA-Seq gene expression level and clinicopathological characteristics were obtained from TCGA database. The mean age of 80 UM patients was 61.65 years old, including 45 males and 35 females. The mean value of tumor diameter and thickness were 16.93 and 10.42 mm respectively. In our study cohort, the pathological type of UM included epithelioid cell dominant type and spindle cell dominant type: 42.5% of tumors were epithelioid cell dominant, and 57.5% were spindle cell dominant. There were 68 (85%) cases without extrascleral extension and 7 (8.75%) cases with extrascleral extension. The cancer status included 61 (76.25%) tumor-free cases and 18 (2.25%) cases with tumor. Pathologic stage II was found in 39 (48.75%) cases, and stage III&IV in 40 (50%) cases. And 27 of 80 (33.75%) cases had metastases, 53 of 80 (66.25%) cases had no metastases. Of 80 cases, 23 (28.75%) cases died of all causes.

Survival Outcomes and Multivariate Analysis Prognostic factors of UM were analyzed using univariate and multivariate Cox regression. The univariate analysis suggested that high SNHG15 expression was a risk factor for death from all causes. Other clinicopathologic variables related to poor prognosis included age, tumor diameter, pathological type, extrascleral extension, cancer status (Table 1). In a multivariate analysis, SNHG15 was an independent risk factor for death from all causes, as was age and pathological type.

SNHG15 Expression Associated with Clinical Pathological Characteristics A total of 80 UM cases with SNHG15 expression data and clinicopathologic characteristics were analyzed from TCGA. Kaplan-Meier survival analysis

Table 1 Prognostic parameters in UM were analyzed using univariate and multivariate Cox regression

Parameters	*n*/mean	Death from all causes					
		Univariate analysis			Multivariate analysis		
		P	HR	95%CI	*P*	HR	95%CI
Age, y	61.65	0.019	1.046	1.008-1.085	0.005	1.064	1.018-1.111
Gender		0.325	0.649	0.274-1.536			
Female	35						
Male	45						
Tumor diameter (mm)	16.93	0.034	1.167	1.011-1.347			
Thickness (mm)	10.42	0.183	1.118	0.949-1.317			
Pathological type		0.001	2.133	1.347-3.379	0.006	1.929	1.212-3.068
Epithelioid cell dominant	34						
Spindle cell dominant	46						
Extrascleral extension		0.008	0.215	0.070-0.667			
No	68						
Yes	7						
Cancer status		0.000	0.118	0.050-0.281			
Tumor free	61						
With tumor	18						
Pathological stage		0.360	0.666	0.279-1.589			
II	39						
III&IV	40						
SNHG15		0.029	0.594	0.373-0.947	0.011	0.525	0.319-0.864
High	40						
Low	40						

UM: Uveal melanoma.

demonstrated that high SNHG15 expression group had a worse prognosis when compared to low SNHG15 expression group (Figure 1A, $P<0.05$). As shown in Figure 1B-1D, SNHG15 was statistically differentially expressed in diverse groups of the tumor pathologic stage (stage II *vs* III&IV, $P=0.0257$), metastasis ($P=0.0071$), living status ($P=0.0017$). To clarify the clinicopathologic impact of SNHG15, we also used logistic regression and concluded that the SNHG15 expression (based on median value of 7.94 FPKM) as a categorical variable was statistically related to clinicopathologic features (Table 2). High SNHG15 expression was significantly related to cancer status, pathologic stage, metastasis, living status in UM (all $P<0.05$; Table 2). These results demonstrated that UM with high SNHG15 expression were prone to progress to cancer status of survival with tumor, a more advanced stage, metastasis and poor living status when compared to the low SNHG15 expression group. However, there was no statistically significant difference in age, gender, tumor diameter, thickness, pathological type, extrascleral invasion.

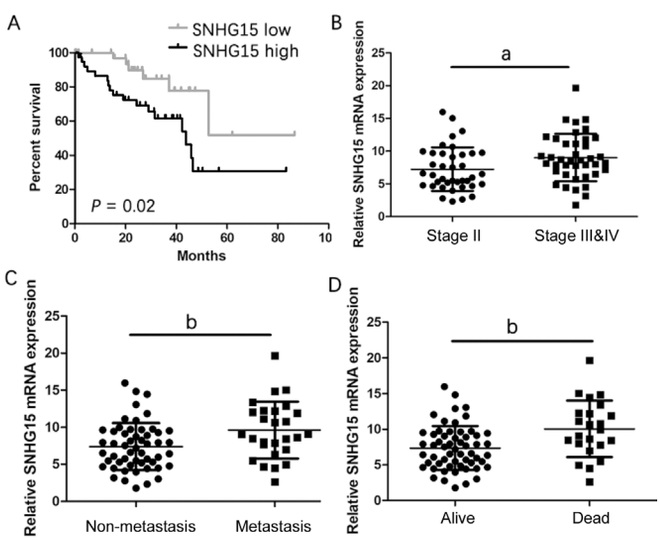

Figure 1 The SNHG15 expression was associated with clinical pathological characteristics A: Patients with high SNHG15 expression had a shorter OS when compared with the low SNHG15 expression group ($P=0.02$); B-D: The expression of SNHG15 was statistically different in diverse groups of the tumor pathologic stage ($P=0.0257$), metastasis ($P=0.0071$), living status ($P=0.0017$). $^aP<0.05$, $^bP<0.01$.

Main Enriched Pathways in UM Tissues with High SNHG15 Expression To explore the SNHG15-related potential signaling pathways activated in UM, GSEA was performed. In the current study, based on the association with SNHG15 expression, the gene list was generated firstly by GSEA. To clarify the statistically significant differences between high and low SNHG15 expression groups, GSEA was

Table 2 Association between SNHG15 expression and clinicopathologic variables using logistic regression

Parameters	*n*/mean	SNHG15 expression		*P*	OR	95%CI
		High	Low			
Age, y	61.65	62.68	60.63	0.509	1.011	0.979-1.043
Gender				0.499	1.357	0.559-3.292
Female	35	19	16			
Male	45	21	24			
Tumor diameter (mm)	16.93	17.56	16.31	0.113	1.115	0.975-1.275
Thickness (mm)	10.42	10.89	9.95	0.135	1.132	0.962-1.332
Pathological type				0.651	1.227	0.505-2.982
Epithelial	34	18	16			
Non-epithelial	46	22	24			
Extrascleral invasion				0.720	0.750	0.156-3.607
No	68	34	34			
Yes	7	4	3			
Cancer status				0.013	0.212	0.063-0.720
Tumor free	61	26	35			
With tumor	18	14	4			
Pathological stage				0.020	0.336	0.135-0.839
II	39	14	25			
III&IV	40	25	15			
Metastases				0.036	0.355	0.135-0.935
No	53	22	31			
Yes	27	18	9			
Living status				0.009	0.239	0.082-0.696
Alive	57	23	34			
Dead	23	17	6			

Table 3 Enriched pathways for differential SNHG15 expression in UM

Name	ES	NES	Nominal *P*-val	FDR *Q*-val
Spliceosome	0.606114	1.607263	0.018256	0.151837
Cell cycle	0.651762	1.670409	0.002028	0.148961
Pyrimidine metabolism	0.581931	1.669619	0.014113	0.113017
DNA replication	0.689555	1.597633	0.030928	0.151044
Nucleotide excision repair	0.675713	1.704181	0	0.129225
RNA degradation	0.663434	1.628078	0.003992	0.179965
Homologous recombination	0.759477	1.724602	0	0.182268
Mismatch repair	0.7302	1.617004	0.01222	0.154619

UM: Uveal melanoma; ES: Enrichment score; NES: Normal enrichment score; FDR: False discovery rate.

conducted subsequently. The results indicated that there were significant differences in spliceosome, cell cycle, pyrimidine metabolism, DNA replication, nucleotide excision repair, RNA degradation, homologous recombination and mismatch repair among patients with high SNHG15 expression phenotype (Figure 2, Table 3).

DISCUSSION

Accumulating evidences indicate that SNHG15 plays a dual role in the tumorigenesis and development of different tumors[26]. Previously, SNHG15 has been demonstrated as a carcinogenic lncRNA, which is usually upregulated in tumor tissues compared with normal tissues[19,27]. It exerts

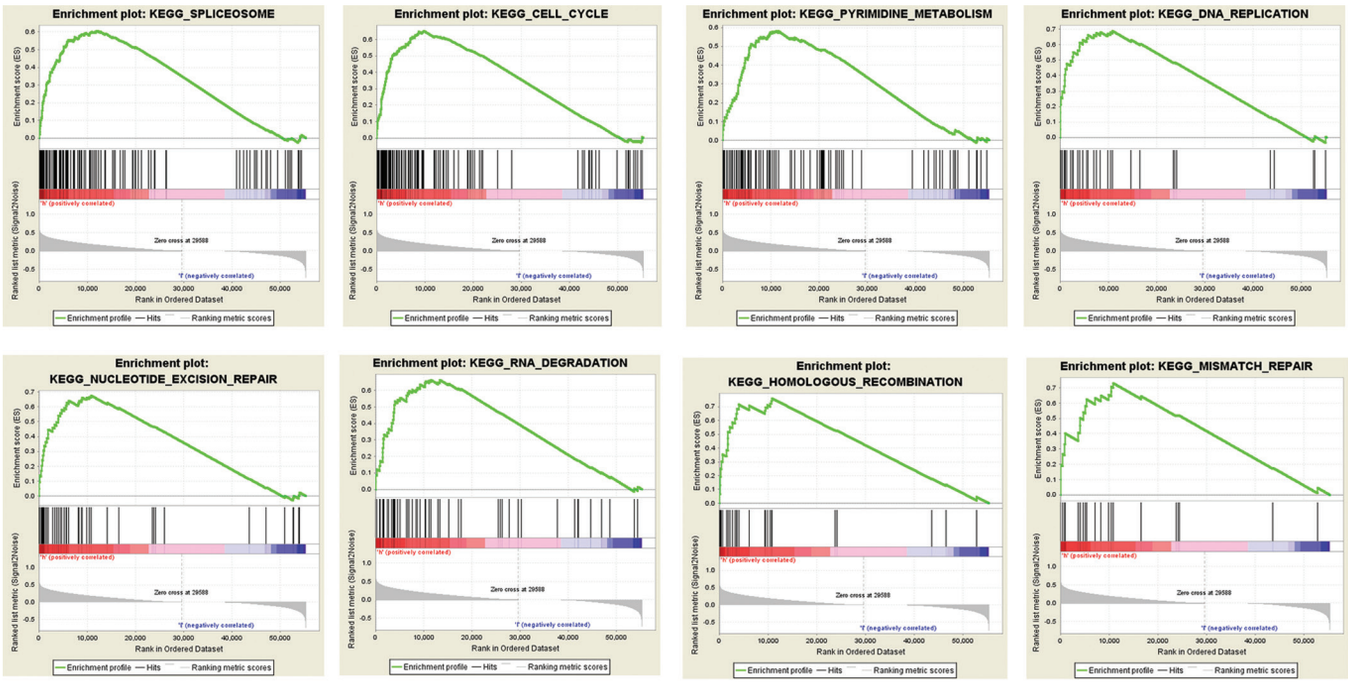

Figure 2 Enrichment plots from GSEA Spliceosome, cell cycle, pyrimidine metabolism, DNA replication, nucleotide excision repair, RNA degradation, homologous recombination and mismatch repair are enriched significantly in SNHG15 high expression phenotype.

an oncogenic effect *via* various epigenetic mechanisms[17,28]. For example, it can suppress the expression of miR-338-3p and facilitate the proliferation of colorectal cancer cells[29]. It plays a carcinogenic role by affecting miR-338-3p/FKBP1A axis in prostate cancer[23]. It can also enhance hepatocellular carcinoma progression by negative regulation of miR-141-3p[21]. However, there are reports that SNHG15 has a tumor suppressive effect, suggesting that low SNHG15 expression is related to poor prognosis in thyroid cancer and upregulating expression of SNHG15 can significantly suppress cell proliferation[30-31]. At present, the impact of SNHG15 on UM is still unclear. Therefore, vital roles and potential biological mechanism of SNHG15 in UM needs to be elucidated.

In this study, we revealed that high SNHG15 expression was related to clinicopathologic features in UM. Through RNA-Seq gene expression level and clinicopathological characteristics obtained from the TCGA UM project, we analyzed the relationship among SNHG15 expression, clinicopathological features and prognosis of UM. The univariate analysis demonstrated that SNHG15 expression level, age, tumor diameter, pathological type, extrascleral extension, and cancer status were risk factors for death from all causes. The multivariate analysis suggested that high SNHG15 expression along with age and pathological type was an independent risk factor for death from all causes. Therefore, the results demonstrated that high SNHG15 expression was an independent predictor of poor prognosis in UM through univariate and multivariate analysis.

Kaplan-Meier survival analysis also indicated that high SNHG15 expression group had a worse prognosis when compared to low SNHG15 expression group in UM. In addition, an analysis was conducted to further explore the relationship between SNHG15 and clinicopathological features. The SNHG15 expression was statistically different in diverse groups of the tumor pathologic stage, metastasis and living status. Besides, high SNHG15 expression (based on median expression value of 7.94 FPKM) in UM was associated with cancer status of survival with tumor, advanced pathologic stage, metastasis and living status. It demonstrated that high SNHG15 expression in UM was strongly related to poor prognosis.

The mechanisms of SNHG15 dysregulation in malignant tumors are quite complex and are far from being completely understood. Previous studies have suggested that SNHG15 is involved in diverse pathological and physiological processes of many tumors through their abnormal expressions, including cell proliferation, invasion, migration and autophagy[17,29]. To explore the biological mechanism of SNHG15 in UM, GSEA was conducted. It indicated that spliceosome, cell cycle, pyrimidine metabolism, DNA replication, nucleotide excision repair, RNA degradation, homologous recombination and mismatch repair were all enriched differentially in SNHG15 high expression phenotype. Alternative splicing is essential for gene regulation, and abnormal splicing plays a vital role in inactivating tumor suppressor genes or activating oncogenes[32]. SNHG15 may have an impact on the invasion

and migration of UM cells by affecting spliceosomal related factors. The abnormal cell proliferation of tumor is related to the lack of checkpoint control over the cell cycle, which is the basis of genetic instability[33]. Evidence shows that the lack of homologous recombination may facilitate the disturbance of cell cycle, the instability and accumulated mutations of genome during the progression and development[34]. Mismatch repair proteins have an significant role in DNA hypermethylation alteration and tumorigenesis[35]. SNHG15 is closely related to DNA replication and mismatch repair, demonstrating that SNHG15 may promote the occurrence of UM by affecting DNA replication and DNA mismatch repair. It indicated that SNHG15 may be identified as a novel marker of diagnosis, therapeutic and prognosis prediction in UM. However, the related mechanism needs to be further elucidated.

This research also has some limitations. The most important one is the limited number of patients and time of follow-up. In addition, some patient characteristics (such as ciliary body involvement) were not completely recorded in the database. In fact, ciliary body involvement plays a critical role in UM[36-37].

In conclusion, this study aims to demonstrate the vital role of SNHG15 in UM and the potential relationship between SNHG15 expression and clinical parameters. SNHG15 expression may be a valuable biomarker for poor survival in UM. Moreover, we have preliminarily explored the crucial pathway associated with SNHG15 in UM. However, further experimental validation is needed to be performed for clarifying the significant impact of SNHG15. And it is of great significance to further identify its independent prognostic value in a large-scale, standardized researches on UM.

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