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ORIGINAL ARTICLE

Identification of Long Noncoding RNA MIR22HG as a Novel Biomarker in Thyroid Cancer

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Abstract

Thyroid cancer (TC) is the one of the most common endocrine malignancy. However, currently there are no specific and sensitive biomarkers for predicting the prognosis for TC. In this study, we for the first time showed MIR22HG was down-regulated in thyroid cancer by analyzing public datasets, including TCGA, GSE29265, GSE33630, and GSE55091. Furthermore, we observed the lower expression levels of MIR22HG were significantly related to higher age, lymph node metastasis status, residual tumor status, N stage, Grade, and T stage in TC. We also observed higher MIR22HG expression was associated with longer overall and disease-free survival time in TC. In order to explore the potential mechanisms of MIR22HG regulating TC progression, 4 hub gene networks regulated by MIR22HG were constructed in the present study. Bioinformatics analysis showed MIR22HG was associated with apoptotic process, regulation of transcription, mRNA splicing, regulation of cell cycle, and Hippo signaling pathway in TC. These results suggested MIR22HG could serve as a novel biomarker for thyroid cancer.

Keywords Thyroid cancer · MIR22HG · Long non-coding RNA · Bioinformatics analysis · Biomarker

Introduction

Thyroid cancer (TC) is the one of the most common endocrine malignancy [1]. In the past decades, the incidence of TC has risen sharply [2, 3]. According to Wanqing et al's report, thyroid cancer had been the most commonly diagnosed cancer before the age of 30 years in females in China [4]. Papillary TC (about 80% of TC) and follicular TC (about 10–15% of TC) account for most TC cases. Despite the 5-year survival rate of papillary thyroid carcinomas (PTCs) can reach up to more than 90%, recurrent disease develops in approximately 20 to 30% of PTC patients. Of note, currently there is no specific and sensitive biomarker for monitoring therapy response or predicting the prognosis for PTC. Thus, exploring new biomarkers for PTC is of great significance to clinical practice.

Long non-coding RNAs (lncRNAs) were a type of ncRNA longer than 200 bps. Previous studies showed lncRNAs played important roles in cancer progression and served as either oncogenes or tumor suppressors. lncRNAs influenced various biological processes, including cell proliferation, metastasis, and therapy-resistant by binding to proteins or miRNAs. For example, a novel lncRNA EPIC1 promoted breast cancer cell cycle progression by interacting with MYC [5], however, lncRNA AC026166.2–001 inhibited laryngeal squamous cell carcinoma proliferation and migration in by regulating the miR-24-3p/p27 axis [6]. Interestingly, emerging evidence revealed lncRNAs could serve as novel biomarkers for cancers. PCA3 levels in serum were associated with high Gleason scores and was a new promising prostate

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cancer biomarker [7–10]. In TC, several lncRNAs (such as LOC100507661 were found to be involved in regulating cell proliferation and migration [11]. However, the roles of lncRNAs in TC remained to be further explored.

In the present study, we explored whether MIR22HG could serve as a biomarker for TC by analyzing public TCGA and GEO datasets. We evaluated the correlations between MIR22HG expression and TC clinical features including age, pathological stage, and recurrence-free survival. In order to explore its potential functional roles in TC, we performed co-expression analysis and GO analysis.

Materials and Methods

TCGA Dataset Analysis

TCGA, GSE29265, GSE50901 and GSE33630 dataset were used to analyze MIR22HG expression levels in thyroid cancer (TC) and normal samples. GSE29265 was uploaded by Tomas which contains 9 anaplastic thyroid carcinomas (ATCs), and 20 papillary thyroid carcinomas (PTCs) paired with their respective adjacent tissues. GSE50901 [12] was uploaded by Barros which contains 61 PTC and 4 adjacent normal thyroid tissue samples. GSE33630 [13] contained 11 ATC, 49 PTC and 45 normal thyroids (N). cBioPortal (http://www.cbioportal.org/) was used to download the expression levels and related clinical information of MIR22HG in TCGA dataset. The 2009 Tumor-Node-Metastasis (TNM) classification was used to evaluate the stage of patients.

Co-expression Network Construction and Analysis

The Pearson correlation coefficient of the SNHG6-gene pair was calculated. The co-expressed SNHG6-gene pair with an absolute Pearson correlation coefficient ≥ 0.3

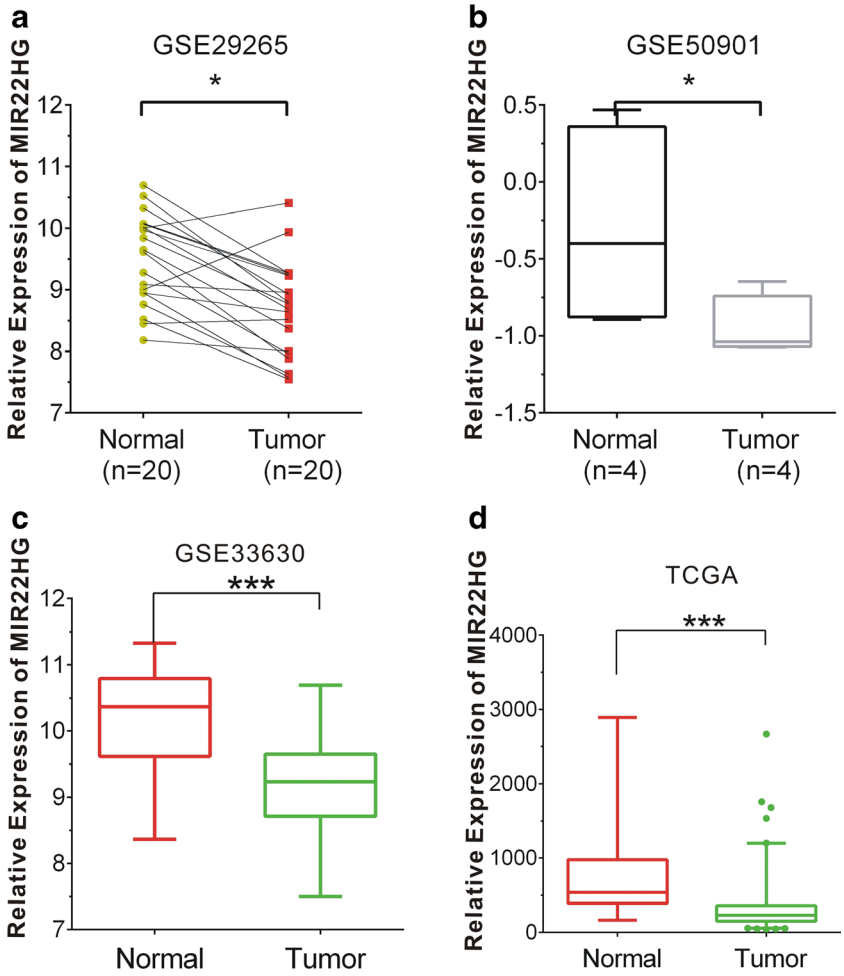

Fig. 1 MIR22HG was downregulated in thyroid cancer. a–d MIR22HG expression levels were significantly down-regulated in TC compared to normal samples by analyzing GSE29265 (**a**, $P < 0.05$), GSE55091 (**b**, $P < 0.05$), GSE33630 (**c**, $P < 0.001$) and TCGA (**d**, $P < 0.001$) datasets. (*, $P < 0.05$. ***, $P < 0.001$)

was selected and a co-expression network was established using Cytoscape.

GO & KEGG Pathway Analysis

GO and KEGG pathway analysis was used to predict the biological function of SNHG6 by using MAS3.0 system (http://bioinfo.capitalbio.com/mas3/). The *p* value of less than 0.05 was selected as significant.

Statistical Analysis

Statistical comparisons between two groups were performed using T-test or Mann–Whitney U-test according to the test condition. For more groups, one-way ANOVA followed by Newman–Keuls posthoc test was used. Kaplan Meier and Cox regression analyses were used to analyze the association between MIR22HG and disease-free survival as well as the prognosis of prostate cancer. The *p* value of less than 0.05 was considered selected as significant. Statistical analysis was performed using the SPSS software package, version 15.0 (SPSS Inc., Chicago, IL).

Results

Long Non-coding RNA MIR22HG was Downregulated in Thyroid Cancer

In the present study, we analyzed four independent datasets, including TCGA, GSE29265, GSE33630, and GSE55091, to analyze MIR22HG expression levels in TC and normal thyroid samples. As shown in Fig. 1, MIR22HG expression levels were significantly downregulated in TC compared to normal samples in these datasets.

Correlations Between MIR22HG Expression and Clinicopathological Features in Thyroid Cancer Specimens

Furthermore, we analyzed correlations between MIR22HG expression and clinicopathological features in thyroid cancer specimens. We observed the lower expression levels of MIR22HG were significantly related to higher age (Fig. 2a), Lymph node metastasis status (Fig. 2b),

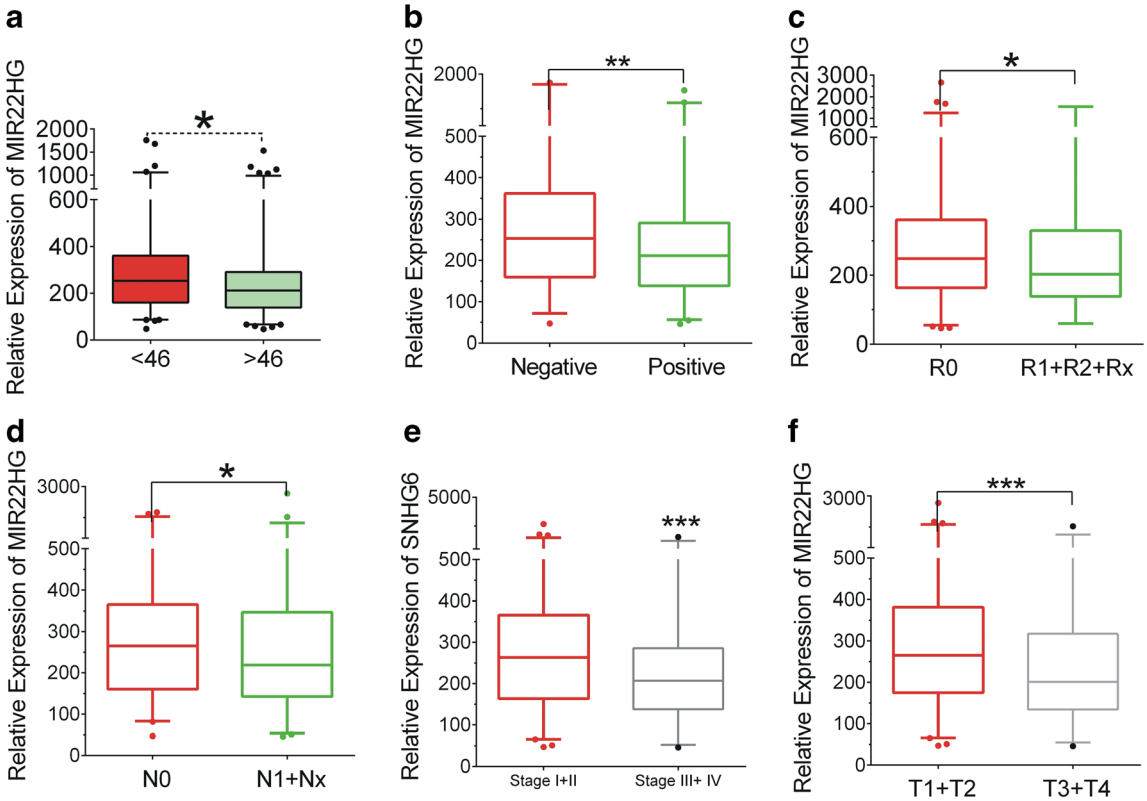

Fig. 2 MIR22HG expression was associated with clinicopathological features in thyroid cancer specimens. a–e The downregulated MIR22HG were significantly related to age (**a**, $P < 0.05$), Lymph node metastasis status (**b**, $P < 0.01$), residual tumor status (**c**, $P < 0.05$), N stage (**d**, $P < 0.05$), higher Grade (**e**, $P < 0.001$) and T stage (**f**, $P < 0.001$). (*, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$)

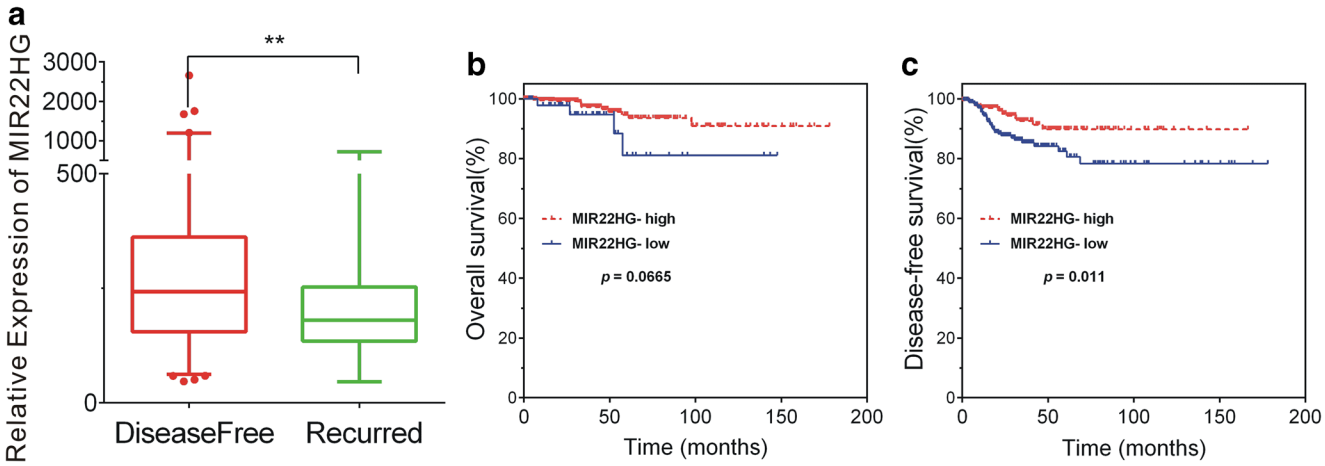

Fig. 3 MIR22HG expression was associated with disease progression. a–c The higher MIR22HG expression was significantly correlated with better disease recurrence rate (**a**, $P < 0.01$), overall survival time (**b**) and disease-free survival time (**c**, $P < 0.05$) in thyroid cancer. (**, $P < 0.01$)

residual tumor status (Fig. 2c), N stage (Fig. 2d), Grade (Fig. 2e) and T stage (Fig. 2f).

In order to further investigate the clinical significance of MIR22HG in thyroid cancer, we performed a Kaplan–Meier

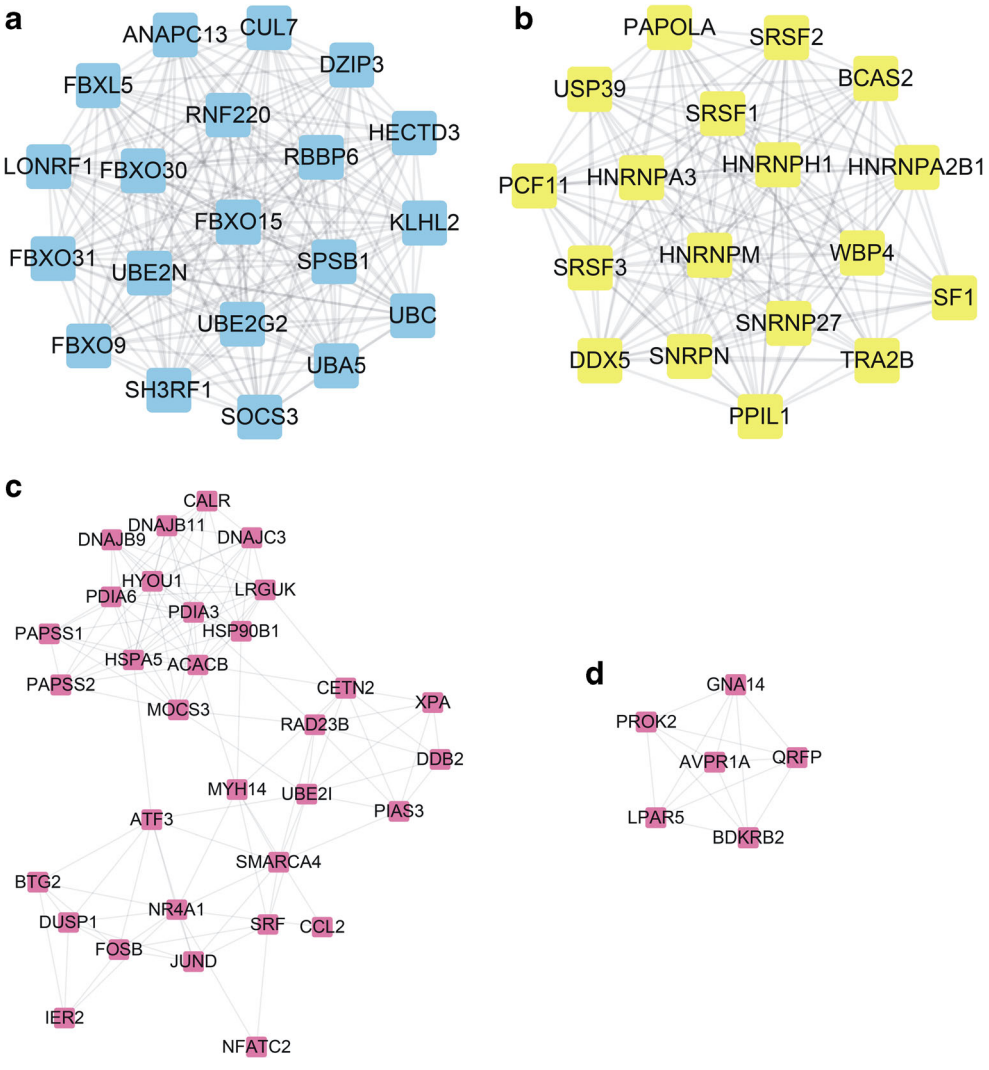

Fig. 4 The top four hub gene networks regulated by MIR22HG in thyroid cancer. a Hub network 1 contained 20 nodes and 190 edges, **b** hub network 2 contained 18 nodes and 147 edges, **c** hub network 3 contained 32 nodes and 129 edges, and **d** hub network 4 contained 6 nodes and 15 edges

analysis. The median expression of MIR22HG in all TC samples was selected as a cutoff to divided TC samples into MIR22HG-high and -low groups. We found higher MIR22HG expression was significantly correlated with better disease recurrence rate (Fig. 3a), overall survival time (Fig. 3b) and disease-free survival time (Fig. 3c) in thyroid cancer. These results suggested MIR22HG could act as a biomarker for thyroid cancer.

Identification of Hub Gene Networks Regulated by MIR22HG in Thyroid Cancer

The functional roles of MIR22HG in TC remained largely unclear. Here, we performed co-expression, GO and KEGG pathway analysis. The top 1000 MIR22HG-mRNA pairs were identified to be reliable according to the absolute value of the Pearson correlation coefficient.

STRING database was further used to identify hub gene networks regulating by MIR22HG in thyroid cancer. Module analysis of the network was performed using the Mcode plugin (degree cut-off ≥2 and the nodes with edges ≥2-core). The top four hub gene networks were shown in Fig. 4. Hub network 1 contained 20 nodes and 190 edges (Fig. 4a), hub network 2 contained 18 nodes and 147 edges (Fig. 4b), hub network 3 contained 32 nodes and 129 edges (Fig. 4c), and hub network 4 contained 6 nodes and 15 edges (Fig. 4d).

Bioinformatics Analysis of MIR22HG in Thyroid Cancer

We next performed GO analysis by using the DAVID system. GO analysis revealed that MIR22HG co-expressed genes were significantly associated with apoptotic process, regulation of transcription, positive regulation of apoptotic process, mRNA splicing, via spliceosome, regulation of cell cycle, response to endoplasmic reticulum stress, skeletal muscle cell differentiation, response to cytokine, IRE1-mediated unfolded protein response, cellular response to hormone stimulus, response to cAMP, global genome nucleotide-excision repair (Fig. 5a). Molecular function analysis showed MIR22HG was involved in regulating ATP binding, transcription factor activity, protein kinase binding, actin filament binding, poly(A) binding, and poly(U) RNA binding (Fig. 5b).

KEGG pathway analysis showed MIR22HG was involved in regulating Hippo signaling pathway, Protein processing in

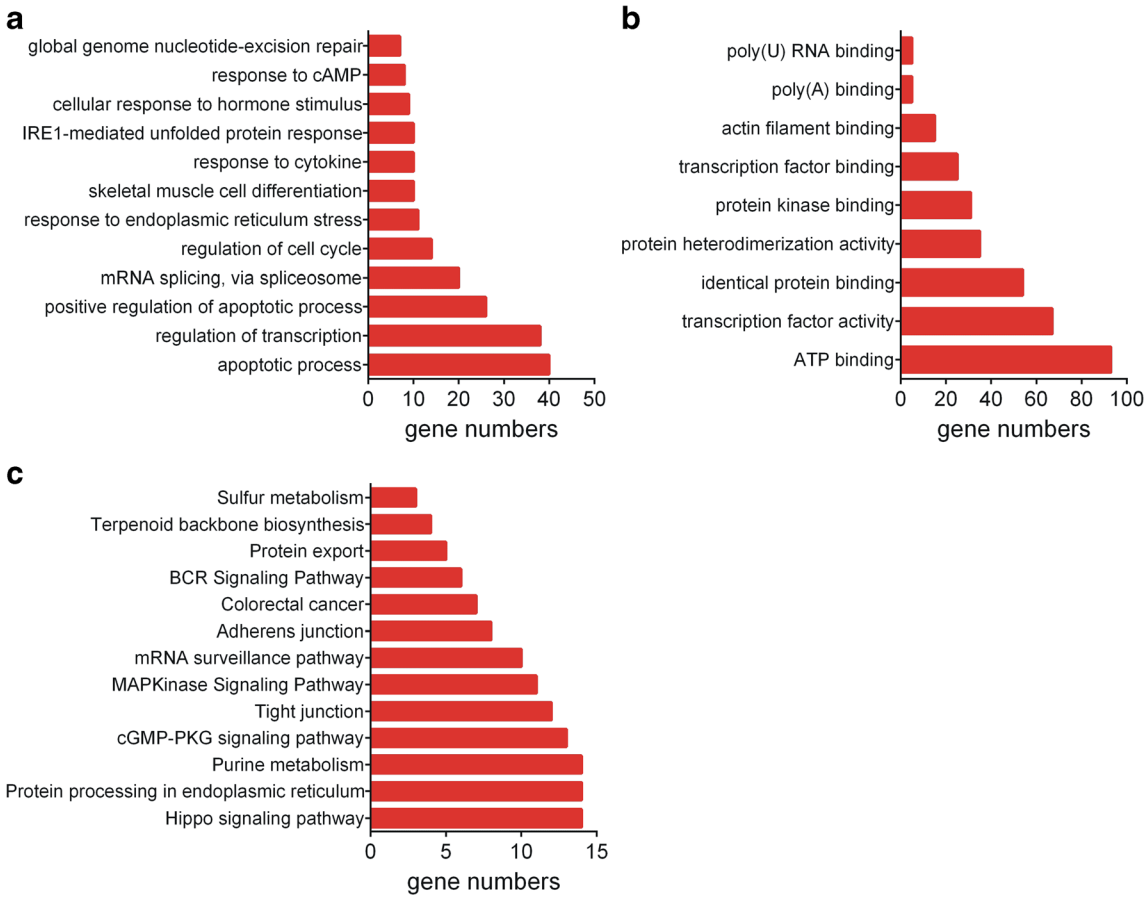

Fig. 5 Bioinformatics analysis for MIR22HG in thyroid cancer. a GO analysis, **b** Molecular function analysis and (**c**) KEGG pathway analysis of MIR22HG co-expressed genes in thyroid cancer

endoplasmic reticulum, Purine metabolism, cGMP-PKG signaling pathway, Tight junction, MAPKinase Signaling Pathway, mRNA surveillance pathway (Fig. 5c).

Discussion

The incidence of TC has risen sharply in the past decade, however, there was still lacking of specific and sensitive biomarker for TC. Previous studies had demonstrated lncRNAs were dysregulated and could predict human cancer outcome. In TC, several lncRNAs were reported to play crucial roles in cancer progression by regulating cell proliferation, invasion, and drug resistance. For example, Hou et al. found lncRNA TNRC6C-AS1 influenced cell proliferation, migration, and invasion by acting as competing endogenous RNA of miR-129-5p to promote UNC5B in thyroid cancer [14]. LncRNA H19 inhibited cell viability and metastasis by downregulating IRS-1 in TC [15]. A novel lncRNA GAS8-AS1 was found to inhibit PTC cell proliferation via regulating ATG5-mediated autophagy [16].

In the present study, we evaluated the prognostic value of MIR22HG in TC by analyzing TCGA and GEO datasets. We for the first time found MIR22HG was downregulated in TC compared to normal samples. Furthermore, we observed MIR22HG expression was significantly correlated with clinicopathological features in TC. MIR22HG was downregulated in high-grade TC samples compared to low-grade TC samples. Kaplan–Meier analysis was performed to evaluate the effect of MIR22HG on TC disease-free survival. We found higher MIR22HG expression was significantly correlated with better disease-free survival time in thyroid cancer. These results suggested MIR22HG could act as a biomarker for thyroid cancer.

MIR22HG was a novel lncRNA involved in several types of human cancer progression, such as endometrial carcinoma and lung cancer. MIR22HG was first reported by Torimura et al., which was involved in responding to chemical stresses (cycloheximide, hydrogen peroxide, cadmium, or arsenic) in hiPSCs [17]. MIR22HG was found to be down-regulated in cancer samples and inhibit cell proliferation. A recent study showed MIR22HG was downregulated and associated with patient survival in lung cancer [18]. Mechanically, MIR22HG could bound and stabilized the YBX1 protein to inhibit cell survival through inhibiting of the oncogenes MET and p21 [18]. However, the roles of MIR22HG in TC remained largely unclear. The present study showed MIR22HG significantly associated with apoptotic process, regulation of transcription, positive regulation of apoptotic process, mRNA splicing, via spliceosome, regulation of cell cycle, and Hippo signaling pathway by performing bioinformatics analysis.

Conclusion

In conclusion, this study for the first time showed MIR22HG was down-regulated in thyroid cancer. Furthermore, we observed the lower expression levels of MIR22HG were significantly related to higher Grade, T stage, N stage and shorter disease-free survival time in TC. Bioinformatics analysis showed MIR22HG was associated with apoptotic process, regulation of transcription, mRNA splicing, regulation of cell cycle, and Hippo signaling pathway. These results showed MIR22HG could serve as a novel biomarker for thyroid cancer.

Authors' Contributions Conception and design: LQ, JZL, CGH; Development of methodology: LQ, JZL, CGH; Analysis and interpretation of data: LQ, JZL, CGH, XLT; Writing, review, and/or revision of the manuscript: LQ, JZL, CGH, XLT.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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