Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Dynamic changes of serum miR-105-3p expression and prognostic value evaluation of postoperative thyroid cancer

Jianping Zhou*, Xiaolong Song, Yufang Li, Yu Song, Long Wei, Ru Yang

Department of Radioimmunity Center, Shaanxi Provincial People's Hospital, Xian, Shaanxi, 710068, China

ARTICLE INFO

Original paper

Article history:
Received: June 06, 2023
Accepted: September 14, 2023
Published: November 30, 2023

Keywords:

Thyroid cancer; serum miR-105-3p; dynamic changes; diagnosis; prognosis

ABSTRACT

Thyroid cancer (TC) originates from thyroid epithelial cells and is one of the common malignant tumors in the endocrine system. The aim of our study was to explore the dynamic changes of serum miR-105-3p expression after TC surgery and its correlation with clinicopathological manifestations, and evaluate its clinical value as a potential biomarker after surgery. A total of 100 TC patients were selected as the research objects. To detect serum miR-105-3p in patients and its correlation with tumor pathological characteristics and the dynamic changes of postoperative serum miR-105-3p in patients to evaluate its prognostic value as a potential biomarker. Serum miR-105-3p increases in patients with well-differentiated TC and lymph node metastasis; Serum miR-105-3p gradually decreases after surgery, and there is a significant difference between 4 days after surgery and before surgery, serum miR-105-3p level can significantly distinguish between patients with poor prognosis and good prognosis within 2 years after the operation, and it can predict the improvement of the prognosis of TC after surgery. The level of serum miR-105-3p is closely related to tumor differentiation and lymph node metastasis in TC patients. Its level gradually decreases with the passage of time after surgery. It has a good diagnostic value for the prognosis of TC after surgery and is expected to become a TC surgery. Potential biomarkers for post-diagnosis.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.12.19

Introduction

Thyroid cancer (TC) originates from thyroid epithelial cells and is one of the common malignant tumors in the endocrine system (1). It has the characteristics of slow growth and low malignancy (2). It has no obvious symptoms when rising early; in the middle and late stages, it can be manifested as hard masses, dysphagia, vocal cord compression, and neck intercourse (3). Symptoms such as compression of nerve nodules seriously dampen patients' quality of life. Epidemiological surveys show that TC accounts for 1.3% of the world's cancer incidence and 0.5% of cancer mortality. TC incidence in China has also been on the rise (4). The number of new cases of TC accounts for 15.6% of the total number of TCs in the world, and the number of deaths accounts for 13.8% of the world's total (5, 6). A large number of clinical research data show that TC is a malignant tumor with a low degree of malignancy and relatively slow development, and the patient has a long survival period and a good prognosis (7). However, it is worth noting that TC has the characteristics of easy recurrence after surgery, which seriously affects the prognosis of patients (8). Therefore, effective risk stratification of TC patients after surgery, so as to timely intervene in patients with high-risk prognosis, can effectively reduce tumor metastasis and recurrence. The probability of improving the prognosis can also effectively save medical resources (9). The current clinical predictive identification of recurrence/metastasis of TC after surgery mainly depends on the detection of relevant serum tumor markers (10, 11). It is vulnerable to the patient's age, gender, endocrine status, intraoperative tumor tissue invasion, and whether to receive radionucleus after surgery. Interference of multiple factors such as thyroid therapy, and related markers are not satisfactory for early judgment of recurrence/metastasis of TC after surgery and for risk stratification (12, 13).

In recent years, the relationship between microRNA (miRNA) and TC has gradually attracted the attention of academic circles. miRNA is a type of small (19-25 nucleotides) non-coding single-stranded RNA with a variety of biological functions (14). As a potential oncogene and tumor suppressor gene, it inhibits the expression of target genes through a post-transcriptional regulatory mechanism and involves tumor development (15, 16). Compared with unaffected thyroid tissue, a variety of miRNAs have been shown to be transcriptionally dysregulated in TC (17-19). Among them, miR-105-3p is a highly conserved miRNA, indicating that it has a variety of potential biological effects (20). miR-105-3p is closely related to tumor onset and development, including ovarian cancer, prostate cancer, colon cancer and hepatocellular carcinoma (21-24). In addition, miR-105-3p can be used as an oncogene to affect various biological behaviors of tumor growth (25). However, to date, little is known about the expression pattern and biological functions of miR-105-3p in TC. This study aimed to investigate the dynamic changes of serum miR-105-3p expression after TC surgery and its correlation with clinicopathological manifestations and to evaluate its clinical value as a potential biomarker.

* Corresponding author. Email: zjpbon868@hotmail.com

Materials and Methods

General information

This study collected 100 TC patients in our hospital from January 2017 to January 2019, all of whom underwent radical resection of TC and were treated with thyroid-stimulating hormone inhibitory drugs after surgery. Collect patient general information (age, gender), pathological type (papillary carcinoma, follicular carcinoma, and medullary carcinoma), tumor differentiation degree (well-differentiated, moderately differentiated, and poorly differentiated), TNM staging, and lymph node metastasis. This study complies with the Declaration of Helsinki and the relevant laws and regulations of China's clinical trial research. All subjects signed an informed consent form or authorized family members to sign before being selected. The research was approved by the hospital ethics committee and complied with the quality management standard requirements of clinical trial research.

Inclusion and exclusion criteria

Inclusion criteria: (1) TC diagnostic criteria based on the 2015 NCCN diagnostic guidelines (26) for TC; (2) age 20-70 years; (3) confirmed by pathological examination; (4) patient has no history of radiotherapy or chemotherapy and endocrine disease. Exclusion criteria: (1) patients with other thyroid surgery; (2) patients with other malignant tumors; (3) patients with immune function diseases; (4) pathological data missing.

Serum miR-105-3p detection

5 mL of fasting peripheral venous blood was collected from all patients 1d before operation and 1d, 2d, 4d, 8d, and 14d after operation, centrifuged at 3000r/min for 10min, and collected serum. Use the Trizol kit to extract serum total RNA, determine RNA purity and concentration, and refer to the reverse transcription kit instruction manual to reverse transcription of RNA into cDNA. ABI7500 fluorescence quantitative PCR instrument was used to determine serum miR-105-3p content.

Follow-up study

After the patient was discharged from the hospital, follow-up was conducted every 6 months, and serum was collected to detect the level of miR-105-3p. All patients were followed up for 2 years after surgery. Recurrence or metastasis was regarded as a poor prognosis, otherwise, the prognosis was good.

Statistical analysis

All data were statistically analyzed using SPSS 22.0 software, and the data were expressed as mean ± standard deviation and a one-way analysis of variance was performed. GraphPad 8.0 software was used for drawing. $p<0.05$ is considered statistically different.

Results

General information

Among all 100 TC patients, 29 were males and 71 were females; aged 20-70 years, with an average (51.92±12.62) years old; pathological types: 38 cases of papillary carcinoma, 33 cases of follicular carcinoma, 29 cases of medullary carcinoma; differentiated degree: 43 cases of high differentiation, 28 cases of moderate differentiation, 29 cases of poor differentiation; TNM staging: 28 cases of stage I, 42 cases of stage II, 30 cases of stage III; lymph node metastasis: 58 cases of lymph node metastasis, 42 cases of no lymph node metastasis (Table 1).

The relationship between preoperative serum miR-105-3p levels and pathological features of TC

We tested the serum miR-105-3p level of all patients 1 day before surgery and found no significant difference in

Table 1. General information on patients with thyroid cancer.

Category	N
Gender	
Male	29
Female	71
Age	
≥60 years old	29
<60 years old	71
Pathological Type	
Papillary carcinoma	38
Follicular carcinoma	33
Medullary carcinoma	29
Differentiation	
Well differentiated	43
Moderate differentiation	28
Poorly differentiated	29
TNM Staging	
Stage I	28
Stage II	42
Stage III	30
Whether Lymph Node Metastasis	
Yes	58
No	42

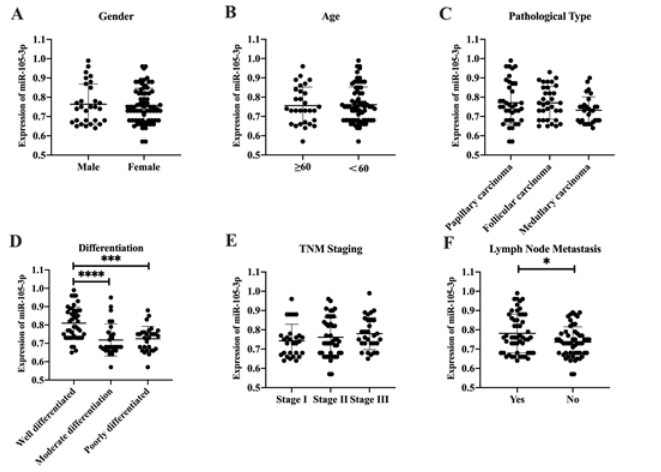

Figure 1. The relationship between preoperative serum miR-105-3p levels and pathological features of TC. (A) Preoperative serum miR-105-3p level in males and females; (B) Preoperative serum miR-105-3p level in ≥ 60 and < 60 patients; (C) Preoperative serum miR-105-3p in different pathological types of TC; (D) Preoperative serum miR-105-3p in differently differentiated TC; (E) Preoperative serum miR-105-3p level in patients in different TNM stages; (F) Preoperative serum miR-105-3p in TC patient with or without lymph node metastasis. Data are expressed as mean±standard deviation; *p<0.05, ***p<0.001, ****p<0.0001.

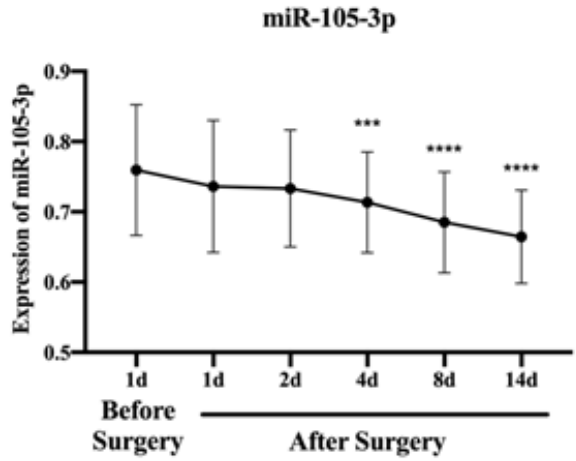

Figure 2. Changes in serum miR-105-3p levels after TC surgery. Data are expressed as mean ± standard deviation; ***p<0.001, ****p<0.0001, compared with 1d before surgery.

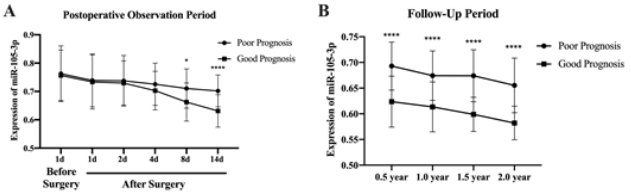

Figure 3. The relationship between serum miR-105-3p level and prognosis after TC surgery. (A) Serum miR-105-3p and prognosis within 14 days after TC surgery; (B) Serum miR-105-3p and prognosis during the 2-year follow-up period after TC surgery. Data are expressed as mean ± standard deviation; *p<0.05, ****p<0.0001, compared with patients with good prognosis.

TC patients of different genders, ages, pathological types and TNM stages (Figure 1A-C and Figure 1E); the serum miR-105-3p level of well-differentiated patients was significantly higher than that of moderately differentiated and poorly differentiated patients (Figure 1D); the serum miR-105-3p level of patients with lymph node metastasis was significantly higher than that of non-metastatic patients (Figure 1D and Figure 1F).

Changes in serum miR-105-3p levels after TC surgery

To study changes in miR-105-3p levels after TC surgery, we detected serum miR-105-3p levels of all patients on the 1d, 2d, 4d, 8d, and 14d post-operatively. The results showed that compared with preoperatively, serum miR-105-3p levels in TC patients showed a decreasing trend after surgery; and with the passage of time after surgery, serum miR-105-3p levels gradually decreased; 4 days after surgery, the patient's serum miR-105-3p level was significantly different from that before surgery (Figure 2).

The relationship between serum miR-105-3p level and prognosis after TC

In order to further explore the relationship between the changes in serum miR-105-3p levels after TC surgery and the patient's prognosis, we conducted a 2-year follow-up of all patients and collected patients' serum for miR-105-3p levels every 6 months, 4 times in total. The results showed that 47 patients had recurrence or metastasis 2 years after surgery, which was a poor prognosis; 53 patients had a good prognosis. Comparing the changes in serum miR-105-3p levels of postoperative patients, it was found that from 8 days after TC surgery, serum miR-105-3p levels can significantly distinguish between patients with poor prognosis and patients with good prognosis (Figure 3A), and during the 2-year follow-up period, the serum miR-105-3p level of patients with poor prognosis was significantly higher than that of patients with good prognosis (Figure 3B).

The diagnostic value of serum miR-105-3p level in the prognosis of TC

The diagnostic value of serum miR-105-3p level on the prognosis of TC was analyzed by ROC curve and AUC. The diagnostic prognostic sensitivity of serum miR-105-3p at 1d, 2d, 4d, 8d, and 14d after operation were 98.11, 96.36, 98.18, 98.18, 96.36, the specificity was 97.87, 97.96, 97.96, 97.96, 97.96, the AUC was 0.53, 0.53, 0.58, 0.68, 0.79, and the 95% confidence intervals were 0.41-0.64, 0.41-0.64, 0.47-0.69, 0.57-0.78, 0.71-0.88, respectively (Figure 4); the diagnostic and prognostic sensitivities of serum miR-105-3p within 2 years were 98.18, 96.36, 98.18, 98.18, the specificity was 97.96, 97.96, 97.96, 97.96, the AUC was 0.82, 0.80, 0.89, 0.88, and the 95% confidence interval was 0.74-0.90, 0.71-0.88, 0.82-0.95, 0.81-0.94, respectively (Figure 5).

Discussion

TC is currently one of the fastest-growing malignant tumors, and its specific pathogenesis is not clear (26, 27). It can be related to many factors such as diet, genetic inheritance, ionizing radiation and chemical substances (28). Current studies believe that the occurrence of TC is related to environmental factors and genetic factors, involving the inactivation of tumor suppressor genes and the excessive

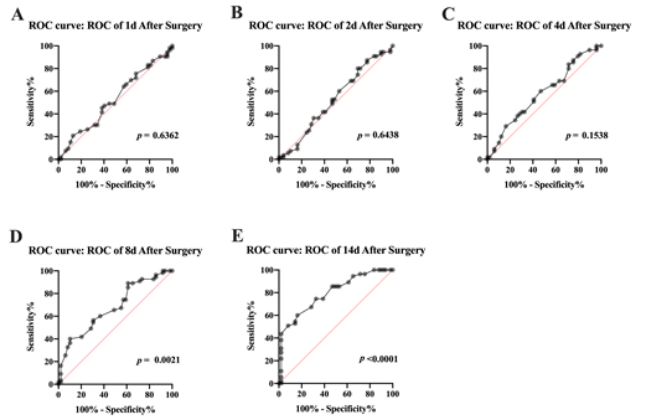

Figure 4. The prognostic value of serum miR-105-3p level after TC surgery. (A-E) ROS curve of 1d, 2d, 4d, 8d, and 14d after TC surgery.

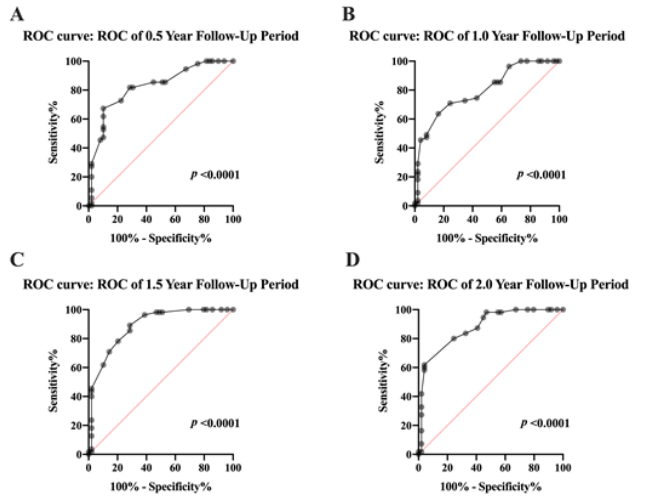

Figure 5. The diagnostic value of serum miR-105-3p level in the follow-up period after TC surgery for the prognosis. (A-D) ROS curve during 0.5-year, 1.0-year, 1.5-year, and 2.0-year follow-up period after surgery.

activation of oncogenes, and multiple signal transduction pathways cause excessive proliferation and apoptosis of tumor cells, thereby promoting tumor development, and the signal transduction pathways in tumor cells are regulated by multiple factors (29). With the gradual development of diagnosis and treatment methods, studies have found that the prognosis of TC is relatively good, but its postoperative evaluation of the prognosis still lacks specific non-invasive detection markers (19, 30). Therefore, this study explored the dynamic changes of serum miR-105-3p expression after TC surgery and its correlation with clinicopathological manifestations and evaluated its clinical value as a potential biomarker after TC surgery.

miRNA is an important molecule that regulates gene expression discovered in recent years (31). Its properties are relatively stable in tumors and the expression of miRNA in different tumor cells or tumor tissues may be different, but they are the same in the same individual. In different tumors, miRNA plays the role of promoting or suppressing cancer, which mainly depends on the downstream transcription RNA, and the relationship between miRNA and its target gene in the body is regulated by various factors (32). The diagnostic value of miRNA in TC has been confirmed (33). It can not only distinguish malignant tissues from normal tissues but also has differential expression in different stages of TC. Assessing serum miRNA levels is a practical method for follow-up patients after noninvasive thyroidectomy (34). Our study found that serum miR-105-3p levels were significantly increased in patients with well-differentiated TC and lymph node metastasis, suggesting that serum miR-105-3p levels are closely related to the degree of differentiation of TC patients and lymph node metastasis. Within 14 days after the operation, the serum miR-105-3p level gradually decreased over time, suggesting that the reduction of serum miR-105-3p level can predict the improvement of the prognosis of TC after surgery.

Postoperative recurrence or metastasis not only increases the treatment difficulty and causes the body to be injured twice, but it is also the main reason for the decrease in the survival rate of patients (35-41). Early prediction of the risk of postoperative recurrence or metastasis of TC helps clinicians formulate effective preventive measures, thereby significantly improving the prognosis of patients and improving the quality of life after surgery (42). Our study found that serum miR-105-3p levels can significantly distinguish patients with poor prognosis and good prognosis 4 days after TC surgery, and the diagnostic value of serum miR-105-3p levels gradually increases with the passage of time after surgery, suggesting that serum miR-105-3p level has a good diagnostic value for the prognosis of TC after surgery and has potential for the diagnosis of TC after surgery.

Conclusion

The level of serum miR-105-3p is closely related to tumor differentiation and lymph node metastasis in TC patients, and its level gradually decreases with the passage of time after surgery. It has a good diagnostic value for the prognosis of TC after surgery and is expected to become a TC surgery. Potential biomarkers for post-diagnosis.

Funding

Application of tumor proliferation markers in postoperative monitoring of differentiated thyroid cancer (No. 2021SF-069).

Competing interests

All authors declare that there is no conflict of interest.

Ethics approval and consent to participate

For human study, written informed consent and approval documents from the Ethics Committee of Shaanxi Provincial People's Hospital were obtained. Written informed consent was obtained from all patients.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

References

1. Asamoah EO, Caraballo G, Castro MR. Identifying and addressing health disparities in thyroid cancer care. J Clin Endocrinol Metab. 2022;107(5):e2190-e2191. doi: 10.1210/clinem/dgab875. PMID: 34871424; PMCID: PMC9016455.
2. Lee AW, Ng WT, Pan JJ, Chiang CL, Poh SS, Choi HC, et al. International guideline on dose prioritization and acceptance cri-

teria in radiation therapy planning for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2019;105:567-580. doi: 10.1016/j.ijrobp.2019.06.2540. PMID: 31276776.
3. Bourlon MT, Barragan-Carrillo R, Mesa-Chavez F, Villarreal-Garza C. Challenges of treating young women with cancer in the era of new oncologic treatments. Rev Invest Clin. 2021;73:302-305. doi: 10.24875/RIC.21000312. PMID: 34609370.
4. Cheng F, Xiao J, Shao C, Huang F, Wang L, Ju Y, et al. Burden of thyroid cancer from 1990 to 2019 and projections of incidence and mortality until 2039 in China: findings from global burden of disease study. Front Endocrinol (Lausanne). 2021;12:738213. doi: 10.3389/fendo.2021.738213. PMID: 34690931; PMCID: PMC8527095.
5. Kong F, Zhou J, Du C, He X, Kong L, Hu C, et al. Long-term survival and late complications of intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. BMC Cancer. 2018;18(1):1139. doi: 10.1186/s12885-018-5055-5. PMID: 30453915; PMCID: PMC6245884.
6. Wirth S, Syleouni ME, Karavasiloglou N, Rinaldi S, Korol D, Wanner M, et al. Incidence and mortality trends of thyroid cancer from 1980 to 2016. Swiss Med Wkly. 2021;151:w30029. doi: 10.4414/smw.2021.w30029. PMID: 34751539.
7. Creff G, Jegoux F, Bendiane MK, Babin E, Licaj I. Social and sexual health of thyroid cancer survivors 2 and 5 years after diagnosis: the VICAN survey. Support Care Cancer. 2022;30(3):2777-2785. doi: 10.1007/s00520-021-06715-7. PMID: 34837541.
8. Al-Kholy AF, Abdullah OA, Abadier MZ, Hassaan MM, Shindy MF, Nor El-Dien DM, et al. Pre-treatment serum inflammatory cytokines as survival predictors of patients with nasopharyngeal carcinoma receiving chemoradiotherapy. Mol Clin Oncol. 2016;5(6):811-816. doi: 10.3892/mco.2016.1041. PMID: 28105362; PMCID: PMC5228416.
9. Moosa NA, Nasser MA, Alshehabi M. Thyroid cancer risk assessment indicators: A correlation between preoperative and postoperative criteria. Neuro Endocrinol Lett. 2021;42(6):417-422. PMID: 34713694.
10. Zahra HO, Omran GA, Gewely AG, Eldehn AF, Abdo W, Elmahallawy EK, et al. Prognostic Value of Serum Thyroglobulin and Anti-Thyroglobulin Antibody in Thyroid Carcinoma Patients following Thyroidectomy. Diagnostics (Basel). 2021;11(11):2080. doi: 10.3390/diagnostics11112080. PMID: 34829426; PMCID: PMC8622548.
11. Chan JY, Wong ST, Wei WI. Whole-organ histopathological study of recurrent nasopharyngeal carcinoma. Laryngoscope. 2014;124(2):446-450. doi: 10.1002/lary.24218. PMID: 23712855.
12. Ratajczak M, Gaweł D, Godlewska M. Novel inhibitor-based therapies for thyroid cancer-an update. Int J Mol Sci. 2021;22(21):11829. doi: 10.3390/ijms222111829. PMID: 34769260; PMCID: PMC8584403.
13. Huang CL, Guo R, Li JY, Xu C, Mao YP, Tian L, et al. Nasopharyngeal carcinoma treated with intensity-modulated radiotherapy: clinical outcomes and patterns of failure among subsets of 8th AJCC stage IVa. Eur Radiol. 2020;30(2):816-822. doi: 10.1007/s00330-019-06500-5. PMID: 31650266.
14. Cao HL, Gu MQ, Sun Z, Chen ZJ. miR-144-3p contributes to the development of thyroid tumors through the PTEN/PI3K/AKT pathway. Cancer Manag Res. 2020;12:9845-9855. doi: 10.2147/CMAR.S265196. PMID: 33116843; PMCID: PMC7553603.
15. Nan BY, Xiong GF, Zhao ZR, Gu X, Huang XS. Comprehensive identification of potential crucial genes and miRNA-mRNA regulatory networks in papillary thyroid cancer. Biomed Res Int. 2021;2021:6752141. doi: 10.1155/2021/6752141. PMID: 33521130; PMCID: PMC7817291.
16. Jin YB, Zhang GY, Lin KR, Chen XP, Cui JH, Wang YJ, et al. Changes of plasma cytokines and chemokines expression level in nasopharyngeal carcinoma patients after treatment with definitive intensity-modulated radiotherapy (IMRT). PLoS One. 2017;12(2):e0172264. doi: 10.1371/journal.pone.0172264. PMID: 28207826; PMCID: PMC5312867.
17. Zhang T, Chen Y, Lin W, Zheng J, Liu Y, Zou J, et al. Prognostic and immune-infiltrate significance of miR-222-3p and its target genes in thyroid cancer. Front Genet. 2021;12:710412. doi: 10.3389/fgene.2021.710412. PMID: 34737762; PMCID: PMC8562566.
18. Wen DY, Pan DH, Lin P, Mo QY, Wei YP, Luo YH, et al. Downregulation of miR-486-5p in papillary thyroid carcinoma tissue: A study based on microarray and miRNA sequencing. Mol Med Rep. 2018;18(3):2631-2642. doi: 10.3892/mmr.2018.9247. PMID: 30015845; PMCID: PMC6102695.
19. Toraih EA, Elshazli RM, Trinh LN, Hussein MH, Attia AA, Ruiz EML, et al. Diagnostic and prognostic performance of liquid biopsy-derived exosomal microRNAs in thyroid cancer patients: a systematic review and meta-analysis. Cancers (Basel). 2021;13(17):4295. doi: 10.3390/cancers13174295. PMID: 34503104; PMCID: PMC8428356.
20. Jabrodini A, Sohrabizdeh M, Aboutalebian S, Hashemi SB, Zomorodian K, Alirezaie A, et al. Molecular strategy for the direct detection and identification of the most common fungal community in cerumen specimens by multiplex PCR. J Med Microbiol. 2023;72(8). doi: 10.1099/jmm.0.001746. PMID: 37624031.
21. Nemati S, Gerami H, Faghih Habibi A, Kazemnejad E, Shabani N, Aghsaghloo V, et al. Sertaconazole versus clotrimazole and miconazole creams in the treatment of otomycosis: a placebo-controlled clinical trial. Iran J Otorhinolaryngol. 2022;34(120):27-34. doi: 10.22038/IJORL.2021.54805.2872. PMID: 35145933; PMCID: PMC8801007.
22. Cui W, Dai J, Ma J, Gu H. circCDYL/microRNA-105-5p participates in modulating growth and migration of colon cancer cells. Gen Physiol Biophys. 2019;38(6):485-495. doi: 10.4149/gpb2019037. PMID: 31829306.
23. Li Y, Liu J, Piao J, Ou J, Zhu X. Circ_0109046 promotes the malignancy of endometrial carcinoma cells through the microRNA-105/SOX9/Wnt/β-catenin axis. IUBMB Life. 2021;73(1):159-176. doi: 10.1002/iub.2415. PMID: 33220169.
24. Anwar K, Gohar MS. Otomycosis; clinical features, predisposing factors and treatment implications. Pak J Med Sci. 2014;30(3):564-567. doi: 10.12669/pjms.303.4106. PMID: 24948980; PMCID: PMC4048507.
25. Sirotkin AV, Lauková M, Ovcharenko D, Brenaut P, Mlyncek M. Identification of microRNAs controlling human ovarian cell proliferation and apoptosis. J Cell Physiol. 2010;223(1):49-56. doi: 10.1002/jcp.21999. PMID: 20039279.
26. Jimenez-Garcia L, Celis-Aguilar E, Díaz-Pavón G, Muñoz Estrada V, Castro-Urquizo Á, Hernández-Castillo N, et al. Efficacy of topical clotrimazole vs. topical tolnaftate in the treatment of otomycosis. A randomized controlled clinical trial. Braz J Otorhinolaryngol. 2020;86(3):300-307. doi: 10.1016/j.bjorl.2018.12.007. PMID: 30826311; PMCID: PMC9422661.
27. Haroon Al Rasheed MR, Xu B. Molecular alterations in thyroid carcinoma. Surg Pathol Clin. 2019;12(4):921-930. doi: 10.1016/j.path.2019.08.002. PMID: 31672298; PMCID: PMC6883923.
28. Moruskar AS, Shinde V, Ingale MH, Krishna AA, Pawar RD. Nanocrystalline silver for the treatment of otomycosis: A retrospective study. Iran J Otorhinolaryngol. 2023;35(127):83-89. doi: 10.22038/IJORL.2023.66805.3303. PMID: 37223402; PMCID: PMC10202168.
29. Wang H, Ma Z, Cheng X, Tuo B, Liu X, Li T. Physiological and pathophysiological roles of ion transporter-mediated meta-

bolism in the thyroid gland and in thyroid cancer. Onco Targets Ther. 2020;13:12427-12441. doi: 10.2147/OTT.S280797. PMID: 33299328; PMCID: PMC7721308.

30. Qin Y. Identification of prognosis-associated biomarkers in thyroid carcinoma by a bioinformatics analysis. Int J Gen Med. 2021;14:5737-5747. doi: 10.2147/IJGM.S327497. PMID: 34557027; PMCID: PMC8454525.
31. Park JL, Kim SK, Jeon S, Jung CK, Kim YS. MicroRNA profile for diagnostic and prognostic biomarkers in thyroid cancer. Cancers (Basel). 2021;13(4):632. doi: 10.3390/cancers13040632. PMID: 33562573; PMCID: PMC7916038.
32. Tabatabaeian H, Peiling Yang S, Tay Y. Non-Coding RNAs: uncharted mediators of thyroid cancer pathogenesis. Cancers (Basel). 2020;12(11):3264. doi: 10.3390/cancers12113264. PMID: 33158279; PMCID: PMC7694276.
33. Urban CF, Ermert D, Schmid M, Abu-Abed U, Goosmann C, Nacken W, et al. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against Candida albicans. PLoS Pathog. 2009;5(10):e1000639. doi: 10.1371/journal.ppat.1000639. PMID: 19876394; PMCID: PMC2763347.
34. Pathakumari B, Liang G, Liu W. Immune defence to invasive fungal infections: a comprehensive review. Biomed Pharmacother. 2020;130:110550. doi: 10.1016/j.biopha.2020.110550. PMID: 32739740.
35. Azizi Dargahlou, S., Iriti, M., Pouresmaeil, M., Goh, L. P. W. MicroRNAs; their therapeutic and biomarker properties. *Cell Mol Biomed Rep* 2023; 3(2): 73-88. doi: 10.55705/cmbr.2022.365396.1085
36. Kanwal, N., Al Samarrai, O., Al-Zaidi, H. M. H., Mirzaei, A., Heidari, M. Comprehensive analysis of microRNA (miRNA) in cancer cells. *Cell Mol Biomed Rep* 2023; 3(2): 89-97. doi: 10.55705/cmbr.2022.364591.1070.
37. Sasani S, Rashidi Monfared S, Mirzaei AR. Identification of some Echinophora platyloba miRNAs using computational methods and the effect of these miRNAs in the expression of TLN2 and ZNF521 genes in different human body organs. *Cell Mol Biomed Rep* 2024; 4(1): 43-53. doi: 10.55705/cmbr.2023.386145.1100.
38. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. Science. 2004;303(5663):1532-1535. doi: 10.1126/science.1092385. PMID: 15001782.
39. Luo X, Wu ACYZYJBZJ. Analysis of risk factors for postoperative recurrence of thyroid cancer. J BUON. 2019;24(2):813-818. PMID: 31128040.
40. Bruns S, Kniemeyer O, Hasenberg M, Aimanianda V, Nietzsche S, Thywissen A, et al. Production of extracellular traps against Aspergillus fumigatus in vitro and in infected lung tissue is dependent on invading neutrophils and influenced by hydrophobin RodA. PLoS Pathog. 2010;6(4):e1000873. doi: 10.1371/journal.ppat.1000873. PMID: 20442864; PMCID: PMC2861696.
41. Branzk N, Lubojemska A, Hardison SE, Wang Q, Gutierrez MG, Brown GD, et al. Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. Nat Immunol. 2014;15(11):1017-1025. doi: 10.1038/ni.2987. PMID: 25217981; PMCID: PMC4236687.
42. Kang SY, Bang JI, Kang KW, Lee HY, Chung JK. FDG PET/CT for the early prediction of RAI therapy response in patients with metastatic differentiated thyroid carcinoma. PLoS One. 2019;14(6):e0218416. doi: 10.1371/journal.pone.0218416. PMID: 31237886; PMCID: PMC6592523.