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

Expression of miR-373 and its predicted target genes E-cadherin and CD44 in patients with laryngeal squamous cell carcinoma

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Received July 27, 2017; **Accepted** December 18, 2017; **Published** December 30, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.12.8

Abstract: Laryngeal squamous cell carcinoma (LSCC) is a genomically complex disease that is difficult to target, and efforts have been made to identify new treatment strategies and molecular markers that might stratify patients and individualize options for treatment. miR-373 has diametrically opposed roles in different stages and types of cancers. miR-373 has been suggested to quantitatively control *E-cadherin* and *CD44* expression. We studied the expression of miR-373, *E-cadherin* and *CD44* in laryngeal squamous cell carcinoma and evaluated the association between the disease and clinical characteristics of patients. Tumor tissues were collected from 24 laryngeal cancer patients. Adjacent normal tissue samples were also obtained as controls. After RNA isolation, we assessed the *miR-373*, *E-cadherin* and *CD44* levels. As endogenous controls, we used the small RNA U6 and GAPDH TaqMan® to normalize the levels of expression of *miR-373*, *E-cadherin* and *CD44*. The fold change in the expression of the genes in larynx tumor and control tissues was calculated using the $2^{-\Delta\Delta CT}$ method. miR-373 was significantly upregulated in seventeen tumor samples compared to controls. However, the expression levels of both *E-cadherin* and *CD44* mRNA were found to be significantly downregulated in tumor versus control regions (p=0.026 and p=0.005, respectively). We did not find any significant difference in the expression levels of miR-373, *E-cadherin* or *CD44* and cancer risk factors. miR-373, *E-cadherin* and *CD44* may be involved in the etiopathogenesis of laryngeal cancer. It can be suggested that *E-cadherin* and *CD44* are functional targets of miR-373, but we need further studies to investigate this hypothesis.

Key words: miRNA; Target genes; Laryngeal carcinoma.

Introduction

Laryngeal squamous cell carcinoma (LSCC) is an aggressive malignancy that constitutes a large part of the malignant type of laryngeal cancers (1-4). LSCC is a multifaceted and genomically complex disease, and rapidly emerging experimental evidence has started to shed light on wide ranging mechanisms that underlie its development and progression (5). It has been increasingly recognized that inactivation of tumor suppressor genes, overexpression of oncogenes, impairment of the apoptotic pathway and dysregulation of microRNAs (miRNAs) are some of the most relevant molecular mechanisms that contribute to cancer progression, resistance against different molecular therapeutics and ineffective clinical outcome (6,7). Data obtained through high-throughput technologies have considerably improved our understanding of the complexity of the protein network that plays a role in cancer processes, and the discovery of miRNAs has added yet another layer of intricacy to the quantitative regulation of the genetic network of cancer-related genes.

miRNAs are a class of approximately 22-nucleotide non-coding RNA molecules that control the expression of a large number of genes by directly binding to the 3' untranslated region (3'UTR) of their target mRNA, resulting in mRNA degradation or translational repression (8-11). miRNA, produced from what was once considered "genomic trash" have been reported to effectively modulate cancer initiation, progression and dissemination (12-14). Aberrant expression of miRNAs has frequently been noted in a number of cancers, such as breast cancer, ovarian cancer, bladder cancer, hepatocellular cancer, colon cancer and head and neck cancer (15-20).

miR-373 may be considered to be a "double edged sword" because of its context-dependent involvement in cancer, both as an oncogene and a tumor suppressor (21). *CD44* is a cell adhesion glycoprotein that is reportedly involved in cell-matrix and cell-cell adhesion and in cellular signaling (22). It is frequently dysregulated in different cancers. miR-373 and miR-520c have been shown to translationally inhibit *CD44* in prostate cancer cells. miR-373 has also been reported to inhibit cancer progression via positive regulation of *E-cadherin*. Certain evidence has emerged emphasizing the fact that the invasive potential of ovarian cancer SKOV3 cells overexpressing miR-373 is notably reduced (23). *E-cadherin* protein levels were substantially increased in miR-373 transfected lung cancer cells (24). miR-373 transfection strongly induced *E-cadherin* levels in pancreatic cancer cells (25).

In this original study, we investigated possible associations between the expression of three key molecules

(miR-373, *E-cadherin and CD44*) and laryngeal cancer risk or progression.

Materials and Methods

Subjects and specimens

Twenty-four patients with laryngeal cancer were enrolled in the study after giving their informed consent. The patients attended the Haydarpasa Numune Training and Research Hospital. Patients' questionnaires, pathology records and laryngoscopy findings were obtained from the medical charts of the patients to confirm the diagnosis and cancer staging. The control subjects, who were not taking any regular medication at the time of the study, were randomly selected among healthy volunteers. Clinical and pathological information on all larynx SCC diagnoses were confirmed by manual review of the pathology reports and endoscopic findings of the Otorhinolaryngology Department. The stages of the laryngeal cancers were defined according to the American Joint Committee on Cancer (AJCC) TNM classification. Glottic and supraglottic tumors were categorized into T1, T2, T3 and T4 subclasses according to the localization of the tumor. Nodal status was categorized as no regional lymph nodes affected (N0), metastasis in a single ipsilateral lymph node, ≤3 cm in the largest dimension (N1) or metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in the largest dimension or multiple lymph nodes ipsi- or contra-laterally (N2a,b,c).

Samples of tumor tissue (2-3 cm long) and the region immediately adjacent to the tumor were collected from the patients. The region immediately adjacent to the tumor was used as the control. All samples were transferred to cryogenic tubes, immediately placed in liquid nitrogen and moved to Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Molecular Medicine, where the experiments were conducted. The study was performed according to the current version of the Declaration of Helsinki. Informed consent was obtained from each patient. The experiments were reviewed and approved by the Committee of Experimental Medicine Research Institute at Istanbul University.

RNA extraction and cDNA synthesis protocol

Samples stored at -80 °C were ground in liquid nitrogen using a mortar and pestle. Total RNA and miRNAs were isolated using the mirVana™ miRNA Isolation Kit (Ambion, Austin, TX, USA) according to the manufacturer's instructions. The purity and quantity of RNAs were assessed using a NanoDrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA).

A High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City CA, USA) was used to synthesize cDNA from total RNA. Each RT reaction contained 10 µl of the RT master mix composed of RT Buffer, dNTP mix, RT random primers, Multiscribe™ Reverse Transcriptase, nuclease-free water and 10 µl/100 ng total RNA. The TaqMan® microRNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA) was used for to prepare cDNA from miRNA samples. RT reactions were performed in a 15-µl volume, and each reaction contained 10 ng of microRNA. A 10-µl reaction mix containing Reverse Transcription (RT) Buffer, dNTP mix, RNase Inhibitor, Multiscribe™ Reverse Transcriptase and nuclease-free water was prepared and mixed with the RT Random Primers and 5µl of RNA template. All reactions were run on the BIO−RAD T100™ Thermal Cycler (Bio-Rad, Hercules, CA, USA). The conditions for the reverse transcription of total RNA samples were as follows: 25 °C for 10 min, 37 °C for 120 min, 85 °C for 5 min, and 4 °C on hold. For synthesis of cDNA from miRNA samples, the following conditions were used: 16 °C for 30 min, 42 °C for 30 min, 85 °C for 5 min, and 4 °C on hold.

Real-time quantitative PCR

A TaqMan® MicroRNA Assay and a TaqMan® Endogenous Control Assay U6 (Applied Biosystems, Foster City CA, USA) were used to detect the miR-373 levels in tumor and control samples. Following the reverse transcription reactions, qPCR amplification was performed. Reactions were carried out in 96-well plates in a total volume of 20 µl containing: 1.33 µl of RT product; 1.0 µl of TaqMan MicroRNA assay composed of the small RNA-specific forward PCR primer, specific reverse PCR primer and small RNA-specific FAM™ dye-labeled TaqMan® MGB probe; 10 µl of 2× TaqMan® Universal PCR Master Mix II; and nuclease-free H_2O to adjust the volume. Each reaction was run in duplicate.

The E-cadherin and CD44 expression levels in tumor and control samples were detected using the TaqMan® Gene Expression Assay (Applied Biosystems, Foster City CA, USA). Twenty microliters of a PCR reaction mixture containing 4 µl of RT product, 1.0 µl of TaqMan® Gene Expression Assay with two primers and one 6-FAM™ dye-labeled TaqMan® MGB probe, 10 µl of 2× TaqMan® Universal PCR Master Mix II and nuclease-free H_2O was prepared. Each reaction was run in duplicate.

Real-time PCR reactions were performed with the Mx3005P Real-Time PCR system (Stratagene, La Jolla, CA USA) with the following conditions; 50 °C for 2 min, 95 °C for 10 min to activate enzyme, 40 PCR cycles of 95 °C for 15 sec, 60 °C for 60 seconds and 4 °C on hold. The levels of the small RNA U6 and GAPDH TaqMan® were quantified using the Taqman® Endogenous Control Assay to normalize the levels of miR-373, E-cadherin and CD44.

Analysis of gene expression

The fold change between the carotid artery plaque tissue and control tissue was calculated using the $2^{-\Delta\Delta CT}$ method (26). Differences in expression levels were denoted as log-transformed ratios to show the fold change.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows version 20.0 software (IBM Corp., Armonk, NY). The values were expressed as the mean±standard deviation (SD). Non-parametric Mann-Whitney –U- test was used to determine the statistical differences for regarded gene expressions among groups. P values less than 0.05 denoted statistical significance.

Table 1. Demographic characteristics of the study groups.

Parameters	Patients (n: 24)
Age (year; mean±SD)	62.12±9.83
Gender (Female/Male)	0/24
Alcohol (-/+)	12/12
Smoking (-/+)	0/24
Grade (G1-G2/G3)	16/8
Lymph Node (N0-N1/N2-N3)	20/4
T Stage (T1-T2/T3-T4)	6/18
Metastasis (-/+)	3/21
Family History (-/+)	10/14

Results

The demographic features of the population studied are reported in Table 1Real-time PCR was used in a molecular analysis to quantitatively measure the relative gene expression levels (as fold change) of miR-373, *E-cadherin* and *CD44* in larynx tumors compared to their respective adjacent region. The miR-373, *E-cadherin* and *CD44* gene expression levels in twenty-four samples were reported individually with respect to those of the control samples (Figure 1). miR-373 appeared to be up-regulated in seventeen samples, while the downregulation of *E-cadherin* and *CD44* was observed in fifteen and nineteen samples, respectively. The *E-cadherin* and *CD44* mRNA expression levels were significantly lower in tumor versus control regions (p=0.026 and p=0.005, respectively). By contrast, the expression of *miR-373* was higher in tumors than in control regions, but without significance (p>0.05).

The correlation between the miR-373, *E-cadherin* and *CD44* expression levels and the clinical parameters of patients were also studied (Table 2). We determined cutoff points for regarded genes by using the sample mean values. Patients with laryngeal cancer were separated into low and high levels of *miR-373, E-cadherin*

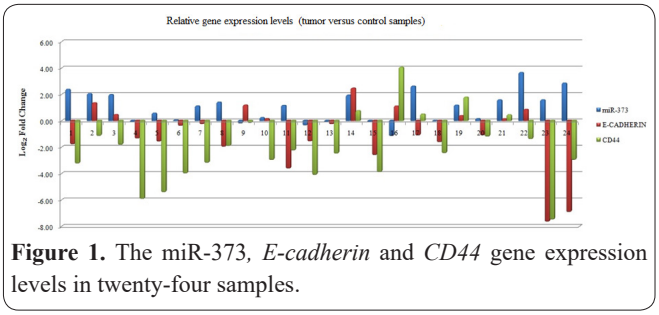

Figure 1. The miR-373, *E-cadherin* and *CD44* gene expression levels in twenty-four samples.

and *CD44* mRNA according to the cut-off values of 1.03, -1.07 and -2.11, respectively. The expression levels of miR-373, *E-cadherin* and *CD44* in patients did not appear to be convincingly associated with cancer risk factors, such as alcohol, smoking, tumor grade, lymph node status, T stage, existence of distant metastases and family history (Table 2).

Discussion

A wealth of information has demystified the substantial role-play of microRNAs in cancer development and progression. miR-373 has been shown to act both as on oncogene and tumor suppressor context-dependently in different cancers.

Exosomes are small membrane vesicles that are 30–100 nm in size and released actively from different cell types, including lymphocytes, dendritic cells and tumor cells by exocytosis (27). It has recently been shown that exosomal miR-373 and miR-200 act as independent prognostic factors for overall survival in epithelial ovarian cancer patients (27).

As far as we know, this is the first study to investigate the possible correlations between the expression levels of miR-373, *CD44* and *E-cadherin* in laryngeal cancer. Upregulated miR-373 levels and simultaneously downregulated levels of *CD44* and *E-cadherin* were noted in our study. The existing data are controversial: some studies confirm our results, but there are also few

Table 2. Correlation of miR-373, E-cadherin and CD44 gene expression with clinical parameters of patients with laryngeal cancer.

Parameters	miR-373 expression		E-cadherin expression		CD44 expression		p-value		
	<1.03 (n=11)	>1.03 (n=13)	<-1.07 (n=12)	>-1.07 (n=12)	<-2.11 (n=13)	>-2.11 (n=11)	miR-373	E-cadherin	CD44
Alcohol	25	75	41.7	58.3	41.7	58.3	>0.05	>0.05	>0.05
Smoking	45.8	54.2	50	50	54.2	45.8	>0.05	>0.05	>0.05
Grade									
G1-G2	50	50	25	75	25	75	>0.05	>0.05	>0.05
G3	45	55	55	45	60	40			
Lymph Node									
N0-N1	50	50	50	50	50	50	>0.05	>0.05	>0.05
N2-N3	25	75	50	50	75	25			
T Stage									
T1-T2	50	50	50	50	66.7	33.3	>0.05	>0.05	>0.05
T3-T4	44.4	55.6	50	50	50	50			
Existence of Distant Metastases									
Yes	33.3	66.7	47.6	52.4	57.1	42.9	>0.05	>0.05	>0.05
No	47.6	52.4	66.7	33.3	33.3	66.7			
Family History of Patients									
Yes	50	50	50	50	57.1	42.9	>0.05	>0.05	>0.05
No	40	60	50	50	50	50			

Values are reported as percentages (%).

studies that contradict them. Huang et al reported that miR-373 and miR-520c have play role as promoting molecule for metastasis in MCF-7 cells. The dowregulation of CD44 may due to miR-373, this may lead to migration phenotype (28). On the other hand, miR-373 are also known as a suppressor of cell migration and invasion and E-cadherin, a regulator of invasion and migration, can be upregulated by miR-373. Some studies showed that the upregulated expression of miR-373 may increase the expression level of E-cadherin (24,25,29). In this study, we have some controversial results. As per literature, if miR-373 was downregulated, then CD44 expression should be high and E-cadherin expression should be low for some cancer types. This is the first study investigating a possible correlation between the difference between miR-373, E-cadherin, CD44 in laryngeal tumours. The aim of the future studies has to justify why and how CD44 expression was not high in larynx tumours. It may be because of mutations in the UTRs of CD44 in the tested samples or there may be an upregulation of another CD44 inhibiting miRNA in those tissues.

Exosomal miR-373 was upregulated in both benign and malignant ovarian tumors. Furthermore, higher levels of miR-373 were associated with a shorter overall survival (27). In breast cancer studies, plasma miR-373 was found to be significantly higher in patients with lymph node metastasis compared with those without lymph node metastasis (30). We could not find any association between miR-373 and the nodal status or any pathological parameters of our patients. The expression levels of plasma miR-373 were found to be significantly higher in breast cancer patients with lymph node metastasis compared with those without lymph node metastasis, suggesting that plasma miR-373 could be used to discriminate the lymph node status of breast cancer (30). The expression levels of both TGFBR2 and *CD44* were notably downregulated in glioma cells reconstituted with miR-373 (31). miR-373 mimics effectively reduced the migratory ability of glioma cells, while the migratory ability was considerably enhanced in cells transfected with anti-miR-373 (31). There was a 5-fold increase in the migratory potential of prostate cancer cells overexpressing miR-373 (22). It has previously been convincingly found that metastasis nodules in the pleura or lungs and bone metastases in the skull developed 6 to 8 weeks after mice were injected with *CD44* shRNA or miR-373- overexpressing cells (28). There is direct evidence suggesting that pomegranate juice considerably inhibits miR-373 in prostate cancer cells (32). Preclinical studies have shown that tumor growth was dramatically enhanced in mice xenografted with *CD44*-silenced pancreatic cancer MIA PaCa-2 cells (33). Testicular nuclear receptor 4 (TR4), a transcriptional regulator, has been noted to modulate cancer formation (34). It has been shown that the expression levels of TGFβR2 and p-Smad3 were notably reduced in TR4-silenced prostate cancer cells. However, their levels increased in prostate cancer cells reconstituted with TR4 (34). Interestingly, the TR4-mediated increase in p-Smad3 and TGFβR2 expression was partially reverted by treatment with miR-373-3p mimics in prostate cancer cells. Metastatic foci formation was notably reduced in mice injected with miR-373-3p and TR4 overexpressing prostate cancer cells (34). There were fewer metastases to organs in female mice 5 weeks after injection in the peritoneal cavity with miR-373-transfected SKOV3^{luc} cells. Rab22a, a member of the Rab family of small GTPases, significantly inhibited the *E-cadherin* levels in ovarian cancer cells (23). Rab22a was itself negatively regulated by miR-373, and both the invasive and migratory potential of Rab22a-overexpressing SKOV3 cells were notably enhanced (23). This study shows that there are some differences between the miRNA expression levels and their targets. This may be related to the dissimilar molecular pathways in cancer. There are some limitations of our study. First, the study is subject to selection bias due to retrospective. Second, the data obtained from a single institution. Third, the number of patients enrolled is relatively small. At last, potential selection bias should not be omitted in thisstudy. Detection the expression levels of these miRNAs and their targets may be promising for the identification of agents for targeting laryngeal cancer specifically and efficiently. In our opinion, miR-373, *CD44* and *E-cadherin* can be important biomarkers either in the diagnosis or progression of cancer. Additionally, it may be effective to investigate the combination of multiple miRNAs, including miR-373, in laryngeal cancer.

Acknowledgements

This work was supported by the Research Council of Istanbul University (project number: 41009 and 23326).

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