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MicroRNA-373 functions as an oncogene and targets YOD1 gene in cervical cancer

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ABSTRACT

miR-373 was reported to be elevated in several tumors; however, the role of miR-373 in cervical cancer has not been investigated. In this study we aimed to investigate the role of miR-373 in tumorigenicity of cervical cancer cells *in vivo* and *in vitro*. The expression of miR-373 was investigated using real-time reverse transcription-polymerase chain reaction assay in 45 cervical specimens and cervical cancer cell lines. The role of miR-373 in tumorigenicity of cervical cancer cells was assessed by cell proliferation, colony formation *in vitro* as well as tumor growth assays *in vivo* with the overexpression of miR-373 or gene silencing. The functional target gene of miR-373 in cervical cancer cells was identified using integrated bioinformatics analysis, gene expression arrays, and luciferase assay. We founded that the expression of miR-373 is upregulated in human cervical cancer tissues and cervical carcinoma cell lines when compared to the corresponding noncancerous tissues. Ectopic overexpression of miR-373 in human cervical cancer cells promoted cell growth *in vitro* and tumorigenicity *in vivo*, whereas silencing the expression of miR-373 decreased the rate of cell growth. YOD1 was identified as a direct and functional target of miR-373 in cervical cancer cells. Expression levels of miR-373 were inversely correlated with YOD1 levels in human cervical cancer tissues. RNAi-mediated knockdown of YOD1 phenocopied the proliferation-promoting effect of miR-373. Moreover, overexpression of YOD1 abrogated miR-373-induced proliferation of cervical cancer cells. These results demonstrate that miR-373 increases proliferation by directly targeting YOD1, a new potential therapeutic target in cervical cancer.

1. Introduction

MicroRNAs (miRNAs) are endogenous 19–25 nt noncoding RNAs that can bind the 3'-untranslated region (3′-UTR) of specific genes to inhibit the translation of corresponding mRNA targets. It has been estimated that miRNAs regulate up to one-third of the total human genes at the posttranscriptional level, indicating that miRNAs have pivotal roles in physiological and pathological processes [1]. Increasing evidence shows that the deregulation of miRNAs plays a significant role in a vast range of biological processes including proliferation, differentiation, and apoptosis [2]. These data highlight the important roles of miRNAs in the development of human tumor and provide new insights into the molecular mechanisms underlying carcinogenesis.

Cervical cancer is the third most common gynecologic cancer in women worldwide. Although screening cervical cancer has been globally popularized, there are still large numbers of advanced diseases, especially in developing countries including China. The molecular pathogenesis of cervical cancer is complicated and poorly understood. Although previous studies have found that 99.7% of cases with cervical cancer can be attributed to human papillomavirus (HPV) infection [3] and several important interactions of E6 and E7 oncoproteins such as AP-1, Bak, c-myc, Epoc-1, E6BP/ERC55, hAda3, IGFBP-3, Mi2, MPP2, NuMA, PDZ, pRb, p21waf1/cip1, p27kip1, p53, and hTERT have been reported to be involved in the development and progression of cervical cancer [4], the roles and potential mechanisms of miRNAs in cervical cancer are still largely unknown. Only few miRNAs such as let-7c, miR-21, miR-34c, miR-199a, miR-200a, and miR-302b have been studied for their roles in the carcinogenesis of cervical cancer [5–7].

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miR-373 was first identified as one of the human embryonic stem cell (ESC)-specific miRNAs.The upregulation of miR-373 has been frequently observed in a number of human cancer types including breast cancer [8], medullary thyroid carcinoma [9], gastric cancer [10], and bladder cancer [11], which suggests that miR-373 functions as an oncogene in tumorigenesis. A previous study demonstrated that the upregulation of miR-373 increased cell proliferation of human testicular germ cell [12] and hepatocellular carcinoma [13,14] *in vitro*. However, Chen et al. reported that downregulation of miR-373 in hilar cholangiocarcinoma is associated with poor cell differentiation, advanced clinical stage, and shorter survival [15]. In our recent study, we detected that downregulations of miR-373 in primary human epithelial ovarian cancer (EOC) tumor were associated with increasing RAB22a status and demonstrated a tumor suppressor role for the miR-373 by targeting Rab22A in human EOC [16]. However, the molecular mechanism by which miR-373 exerts its functions in cervical cancer cells is not clear. In this study, it was demonstrated for the first time that miR-373 is pathologically upregulated in cervical cancer specimens and cell lines, and that ectopic expression of miR-373 promoted cervical cancer cell growth *in vitro* and tumorigenicity *in vivo*. Moreover, YOD1 was identified as the direct functional target of miR-373 in cervical cancer.

2. Materials and methods

2.1. Patients and samples

The samples of cancer tissue were collected from 45 patients with cervical squamous cell carcinoma with FIGO (Federation of Gynecology and Obstetrics) stage IB1-IIA2 who underwent radical hysterectomy between 2010 and 2013 in Department of Obstetrics and Gynecology, Ren-Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. None of the patients received radiotherapy and chemotherapy before the tissues were obtained. The corresponding adjacent normal tissues from the same 45 patients with cervical cancer were obtained 3 cm beyond the boundary of cervical cancer tissues, and normal cervical tissues from 10 control patients who underwent total hysterectomy due to uterine fibroids and endometriosis were also obtained. All specimens were obtained during surgery, frozen immediately in liquid nitrogen, and stored at −80 °C until analysis. The collection of all samples was approved by the Ethical Committee for Clinical Research of the Hospital, and informed consents were obtained from all the patients.

2.2. Cell lines

The human cervical carcinoma cells (HeLa, SiHa, CaSki, and C33A) and human embryonic kidney (HEK293T) cells were obtained from the American Type Culture collection (ATCC, Manassas, VA) and propagated under standard conditions as recommended by the ATCC. All the cell lines were maintained at 37 °C in a humidified atmosphere with 5% CO_2.

2.3. Extraction of RNA and quantitative reverse transcription-polymerase chain reaction

Total RNA was extracted using the TRIzoL reagent (Applied Biosystems, Foster City, CA). cDNA was synthesized using Reverse Transcription Kit (Applied Biosystems). Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analyses for genes were performed with the SYBRGreen PCR Master mix (Applied Biosystems) on an ABI 7300HT real-time PCR system (Applied Biosystems) and GAPDH was used as an internal control. The data analysis was performed using the $2^{\Delta\Delta CT}$ method as $\triangle\triangle CT = (CT_{Target1} - CT_{GAPDH}) - (CT_{Target2} - CT_{GAPDH})$.

The miRNA fraction in cell lines was extracted using miRNA isolation kit (Applied Biosystems). miRNA-specific reverse transcription was performed with TaqMan® MicroRNA Reverse Transcription Kit (Applied Biosystems). qRT-PCR was performed using TaqMan® Universal PCR Master Mix (Applied Biosystems) and U6 small nuclear RNA was used as an internal control.

2.4. Construction and transfection of plasmids

The human pre-miR-373 sequence and human YOD1 sequence were amplified from normal human genomic DNA and cloned into pMSCV vector to generate pMSCV-miR-373 and pMSCV-YOD1. For stable transfection, virus particles were harvested from HEK293T cells 48 h after transfection with pMSCV-miR-373 or pMSCV-YOD1 with the packaging plasmids using Lipofectamine 2000. SiHa cells were infected with virus supernatant fluid with 8 μg/mL polybrene and selected in puromycin for 72 h as 1.5 mg/mL to generate cell lines SiHa-pMSCV-miR-373, SiHa-pMSCV-YOD1, and control cell lines SiHa-pMSCV-NC. Anti-miR-373 inhibitor (anti-miR-373) and negative control (anti-miR-NC) were purchased from Ambion Life Technologies (Foster City, CA) and YOD1 siRNAs were purchased from GenePharma (Shanghai, China). CaSki cells were transiently transfected with oligonucleotide using Lipofectamine 2000 (Invitrogen, Carlsbad, CA).

In the luciferase reporter vector, the wild-type or mutant 3′-UTR of YOD1 was cloned into the downstream of the renilla luciferase gene in the psiCHECK2 vector (Promega, Madison, WI). Other potential target genes were cloned in a similar manner.

2.5. Luciferase assay

After 48 h of transfection, cells were lysed with 1 × reporter lysis buffer, and firefly and renilla luciferase activities were measured using the Dual-Luciferase Reporter Kit (Promega) according to the manufacturer's instructions. Firefly luciferase activity was standardized to the renilla activity as control.

2.6. Cell proliferation assay and colony formation assay

For the cell proliferation assay, 5000 cells were seeded in triplicate in 24-well plates, and viable cells were counted every day using the trypan blue dead cell exclusion dye (Sigma–Aldrich). For the colony formation assay, 500 cells were seeded in triplicate into 6-cm plates and after 10 days, the cells were washed with phosphate-buffered saline (PBS), fixed with frozen methanol, and stained with 0.1% crystal violet (Sigma–Aldrich). The number of positive-staining colonies was counted.

2.7. In vivo proliferation assays

Female BALB/c nu/nu mice aged 4 weeks were kept under pathogen-free conditions according to Shanghai Medical Experimental Animal Care guidelines. Animal protocols were approved by the Institutional Animal Care and Use Committee of Shanghai JiaoTong University School of Medicine. Ten mice in each group were subcutaneously (s.c.) injected with 5×10^6 SiHa-pMSCV-miR-373 in 200 μL PBS per site into both flanks and SiHa3-pMSCV-NC cells as a control. Mice were monitored for tumor growth and weight every 3 days and killed at 30 days after injection. Tumor volume was calculated using caliper to measure the shortest (A) and longest (B) tumor diameters. The formula $V = (A^2 \times B)/2$ was used to calculate tumor volume.

2.8. Western blotting

Cells were lysed with 1 × sodium dodecyl sulfate (SDS) and proteins were separated on 8–15% SDS-polyacrylamide gel electrophoresis. Immunoblots were performed using primary mouse monoclonal antibodies YOD1 and β-actin (Sigma–Aldrich). Then, the blots were incubated using horseradish peroxidase-linked secondary antibody (Abcam). The signals were detected using Chemiluscent ECL Detection system (Millipore, Billerica, MA) and the results of Western blots were analyzed using the Image J program.

2.9. Microarray analysis

The SiHa cells were transfected with pMSCV-NC vector and pMSCV-miR-373 as described above. Total RNA was isolated and labeled. The 35k human Genome array (CapitalBio, Beijing, China) was used for gene expression analysis. The microarray data were analyzed using SpotDataT Pro V3.0. Differentially expressed genes were identified through the fold change set at <0.5-fold (down-regulated) or >2-fold (upregulated) change. Microarray analysis was performed using one biological replicate.

2.10. Statistical analysis

All the experiments were performed at least in triplicate. The data are presented as the mean ± standard deviation. The differences between two groups were analyzed using the two-sided Student's t-test. The statistical analyses of cases in groups were performed using the Chi-square test. $P < 0.05$ was used to indicate a statistically significant difference.

3. Results

3.1. Expression of miR-373 is markedly upregulated in cervical cancer specimens

The expression of miR-373 was detected in 45 pairs of human cervical cancer and adjacent normal tissues by real-time qRT-PCR. As shown in Fig. 1A, the miR-373 was markedly upregulated in cervical cancer samples when compared with adjacent normal tissues and normal cervical samples ($P < 0.01$). When patients with cervical cancer were divided into two groups based on tumor size (i.e. <4 and ≥4 cm), the results imply that the expression of miR-373 increased with increasing tumor size ($P < 0.05$, Table 1). No significant association was found between the expression of miR-373 in age, tumor differentiation, lymph node metastasis, and HPV infection in cervical cancer ($P > 0.05$, Table 1). These results suggested a possible association between the upregulated expression of miR-373 and tumor size in cervical cancer, and miR-373 may be involved as an oncogene in the tumorigenesis of cervical cancer.

In addition to cervical cancer tissues, endogenous expression of miR-373 was detected in a panel of cervical cancer cell lines (HeLa, SiHa, CaSki, and C33A). It was observed that the highest expression of miR-373 was in CaSki cells and the lowest was observed in SiHa cells (Fig. 1B). Given the above results, it was decided to use the CaSki and SiHa cells for the below experiments.

3.2. miR-373 regulates the growth of cervical cancer cell lines in vitro and in vivo

To better understand the impact of miR-373 on the proliferation of cervical cancer cells, the expression of miR-373 was exogenously upregulated in SiHa cells and the expression of miR-373 was downregulated in CaSki cells, in which endogenous miR-373 was expressed at a low level or high level respectively, using a lentivirus vector expressing miR-373 (pMSCV-miR-373) or anti-miR-373 inhibitor. The proliferation of cervical cancer cells affected by miR-373 was monitored using a cell growth curve. As shown in Fig. 1C, overexpression of miR-373 can significantly promote the proliferation of SiHa cells ($P < 0.05$), whereas anti-miR-373 inhibitor-mediated silencing of miR-373 decreased the growth of CaSKi cells ($P < 0.05$). Furthermore, overexpression of miR-373 could significantly promote the tumorigenicity of SiHa cells in nude mice, and the tumor volume of the miR-373 overexpression group was significantly increased compared to the control group ($P < 0.05$, Fig. 1D). Collectively, these data indicated that miR-373 exerts a growth-promoting function in human cervical cancer.

3.3. miR-373 downregulates the expression of YOD1 by targeting the 3′-UTR

Given that miR-373 may execute its growth-promoting function by downregulating the expression of its downstream target genes that normally have tumor-suppressive effect, the microarray gene expression profiling in SiHa-pMSCV-miR-373 cells and SiHa-pMSCV-NC cells was performed. The results in two independent experiments showed that the expression of 156 genes is suppressed by the overexpression of exogenous miR-373 in SiHa cells (Supplementary data). In addition, three bioinformatics-based prediction analysis softwares (PicTar, TargetScan, and miRanda) were used to identify the potential miR-373 targets. Seven potential genes (CDH1, MY1OD, ELAVL2, CDCA7, GALNT3, GNPDA2, and YOD1) were selected. To validate these candidates, dual luciferase reporter assays were performed using constructs in which these targeting sites were cloned into the 3′-UTR of the renilla luciferase reporter gene (psiCHECK™-2). Transfection of SiHa cells with pMSCV-miR-373 resulted in reduced ($P < 0.05$) luciferase activities of ELAVL2, GALNT3, GNPDA2, and YOD1 compared with controls (Fig. 2A). Additional examination of these four genes using qRT-PCR analysis showed that only YOD1 was downregulated in SiHa-miR-373-transfected cells (Fig. 2B).

To further examine YOD1 as a direct target gene of miR-373, dual luciferase reporter assays were performed, which confirmed that the luciferase activities of YOD1 3′-UTR were significantly reduced in SiHa cells stably transfected with pMSCV-miR-373 (Fig. 2C). Based on the bioinformatics prediction analysis, five miR-373-targeting sequences were identified in the 3′-UTR of YOD1 mRNA (Fig. 2D), and mutant vectors of YOD1 3′-UTR containing five mutated bases on the predicted binding sites were constructed. Transient transfection of SiHa cells with those wild-type or mutant vectors and miR-373 or mock control resulted in partial rescue of the inhibition (Fig. 2E), further supporting that YOD1 is a direct target of miR-373.

3.4. Downregulation of YOD1 is inversely correlated with the expression of miR-373 in cervical cancer

To further evaluate the relationship between miR-373 and YOD1 in human cervical cancer, the expression of YOD1 was detected in 45 cervical cancer samples and 10 normal cervical samples using qRT-PCR. The mRNA levels of YOD1 in all investigated cervical cancer tissues were significantly decreased when compared with normal cervical samples (0.3409 ± 0.1233 *vs* 0.7284 ± 0.1701, $P < 0.05$). This downregulation of YOD1 was strongly correlated with the upregulated expression of miR-373 in 45 cervical cancer tissues ($r = 0.6552$, $P < 0.05$), suggesting that downregulation of YOD1 might result from the overexpression of miR-373 in human cervical cancer.

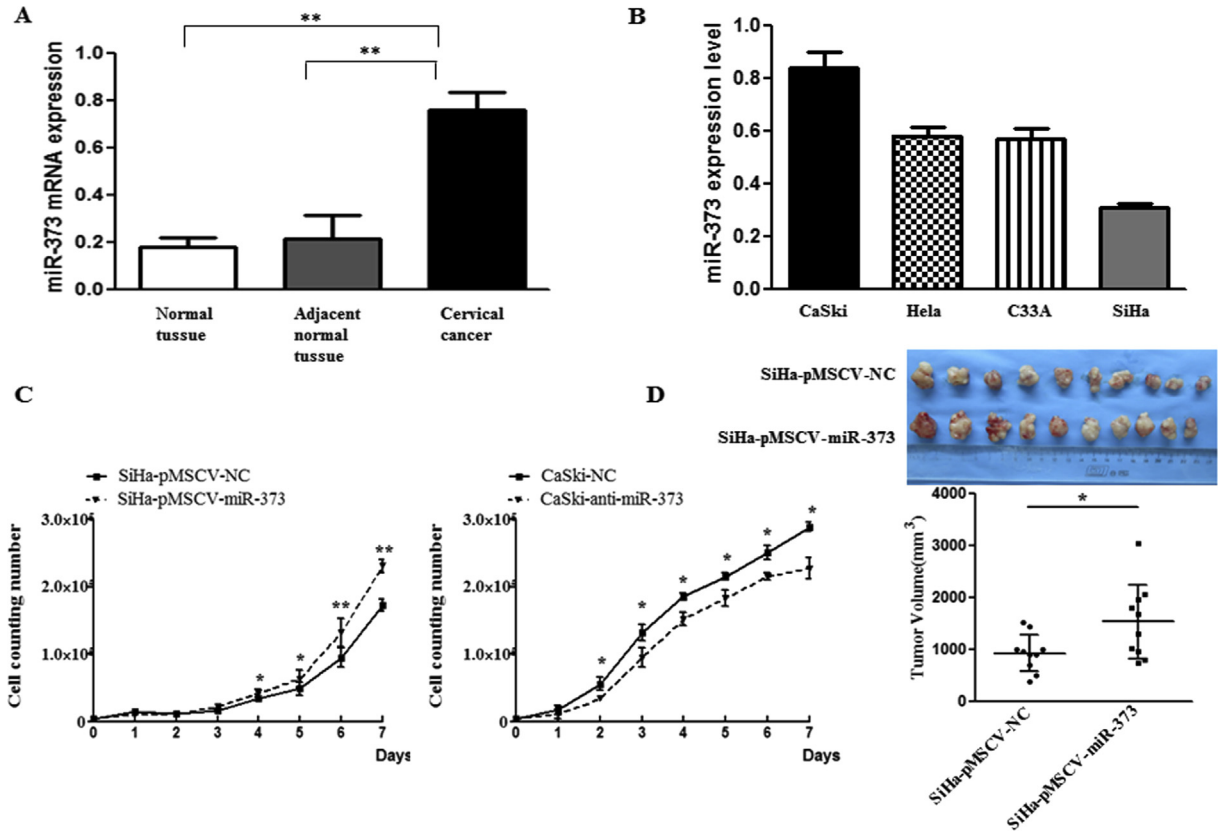

Fig. 1. miR-373 is upregulated in cervical cancer tissues and enhances cervical cancer cell growth *in vitro* and *in vivo*. (A) miR-373 was upregulated in cervical cancer tissues as compared with normal cervical tissues and adjacent normal tissues, $^{**}P < 0.01$. (B) RT-PCR analysis of miR-373 in human cervical cell lines (HeLa, SiHa, CaSki, and C33A). The expression of miR-373 was the lowest in SiHa cells and the highest in CaSki cells. The data represent the mean ± SD of three different experiments. (C) Overexpression of miR-373 promoted the proliferation of SiHa cells and the knockdown of miR-373 resulted in decreased growth rate of the CaSki cells ($^{*}P < 0.05$, $^{**}P < 0.01$). (D) Overexpression of miR-373 significantly promoted the tumor formation of SiHa cells in a nude mouse xenograft model, and the tumor volume of the miR-373 overexpression group (SiHa-pMSCV-miR-373) was significantly increased compared to the control group (SiHa-pMSCV-miR-NC, $P < 0.05$). RT-PCR, reverse transcription-polymerase chain reaction; SD, standard deviation.

3.5. miR-373 directly targets YOD1 to promote tumor proliferation in cervical cancer

To examine whether YOD1 might function in miR-373-induced proliferation of cervical cancer cells, the expression of YOD1 was inhibited with siRNA in CaSKi cells, and co-transfection experiments using anti-miR-373 and siRNA-YOD1 showed that silencing miR-373 could not repress proliferation in YOD1-depleted CaSKi cells (Fig. 3A). In addition, it was revealed that the overexpression of YOD1 could significantly abrogate miR-373-induced cell growth in SiHa cells (Fig. 3B). Taken together, these results proved that miR-373 promotes the proliferation of cervical cancer cells via directly targeting YOD1.

Table 1
Association between miR-373 expression and clinicopathological features of human cervical cancers.

Clinicopathological features	N	miR-373 expression	P Value
Age			
<50	20	0.7984 ± 0.0673	>0.05
≥50	25	0.8252 ± 0.0839	
Tumor size (cm)			
<4.0	20	0.6447 ± 0.0679	<0.05
≥4.0	25	0.8716 ± 0.1085	
Histology			
Well differentiated	16	0.7249 ± 0.0620	>0.05
Moderately differentiated	10	0.8016 ± 0.1302	
Poorly differentiated	19	0.7925 ± 0.0323	
Lymph node metastasis			
No	35	0.8316 ± 0.1185	>0.05
Yes	10	0.7677 ± 0.0179	
HPV			
(−)	7	0.7429 ± 0.0114	>0.05
(+)	38	0.7716 ± 0.1255	

4. Discussion

Recent studies have shown that miRNAs play an important role in carcinogenesis including cervical cancer [17]. However, their molecular mechanism remains largely unknown because of the limited understanding about miRNA target genes. A number of published studies have reported that miR-373 was frequently upregulated in several tumors. However, no information about the function or molecular mechanism of miR-373 in human cervical cancer has been reported. In this study, it was showed that the expression level of miR-373 was significantly higher in human cervical cancer tissues than that of adjacent normal tissues and normal cervical tissues. In functional studies, it was found that the overexpression of miR-373 significantly promotes the proliferation of cervical cancer cells *in vitro* and *in vivo*. Moreover, YOD1 was identified as a direct functional target of miR-373 in cervical cancer.

YOD1 is a highly conserved deubiquitinating enzyme of the ovarian tumor (otubain) family that removes ubiquitin residues from poly-ubiquitinated proteins. Although highly conserved, the function of YOD1 is not known in higher eukaryotes. YOD1 is the closest homolog of *Saccharomyces cerevisiae* Otu1, which associates

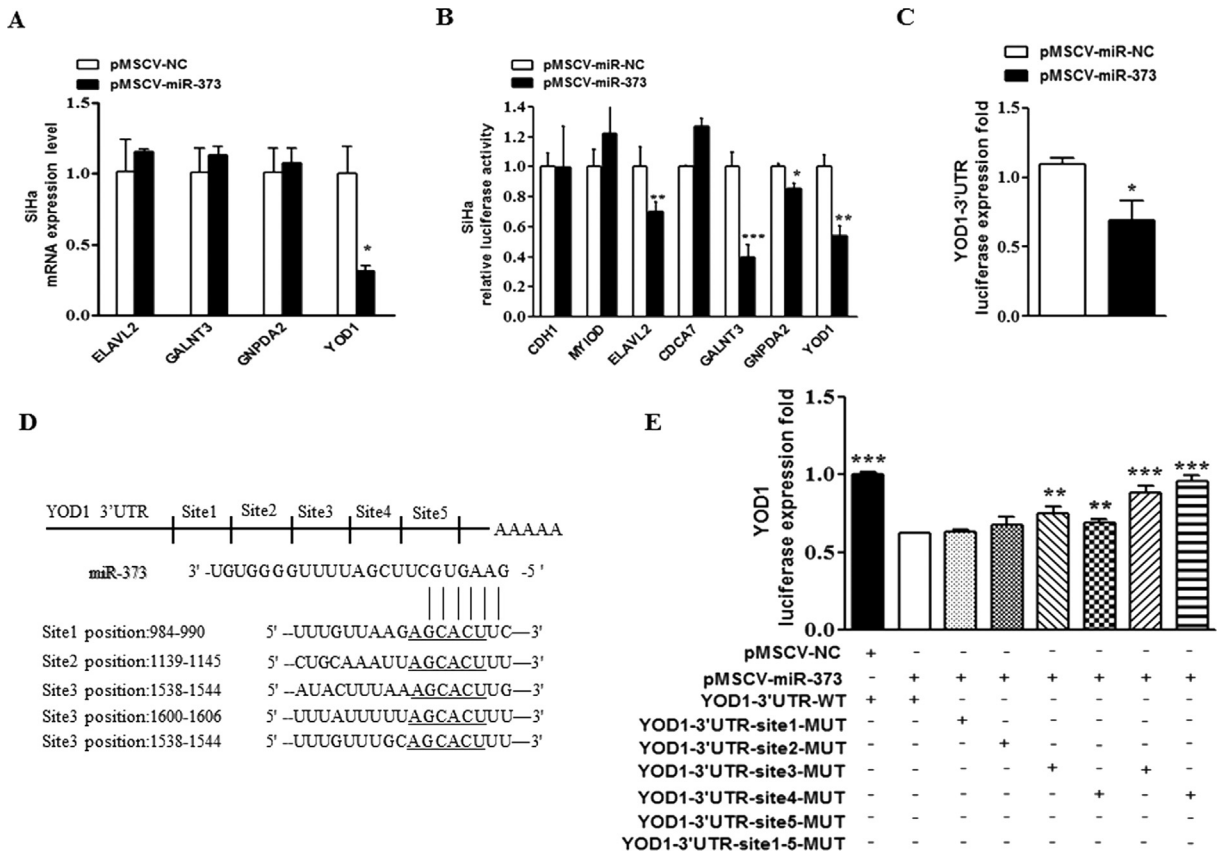

Fig. 2. miR-373 directly regulates YOD1 in SiHa cells. (A) Luciferase reporter assay was used to reveal 3′-UTRs of four candidate miR-373 targets (ELAVL2, GALNT3, GNPDA2, and YOD1). (B) Quantitative RT-PCR was used to validate that only YOD1 was downregulated in miR-373-transfected cells out of the four candidate genes. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. (C) Relative luciferase activity of YOD1 3′-UTR in SiHa cells stably transfected with pMSCV-miR-373. (D) Putative miR-373 binding sequence in the 3′-UTR of YOD1 mRNA. (E) Relative activity of the luciferase gene fused with the wild-type or mutant 3′-UTR of YOD1. $^{*}P < 0.05$, $^{**}P < 0.01$. RT-PCR, reverse transcription-polymerase chain reaction; UTR, untranslated region.

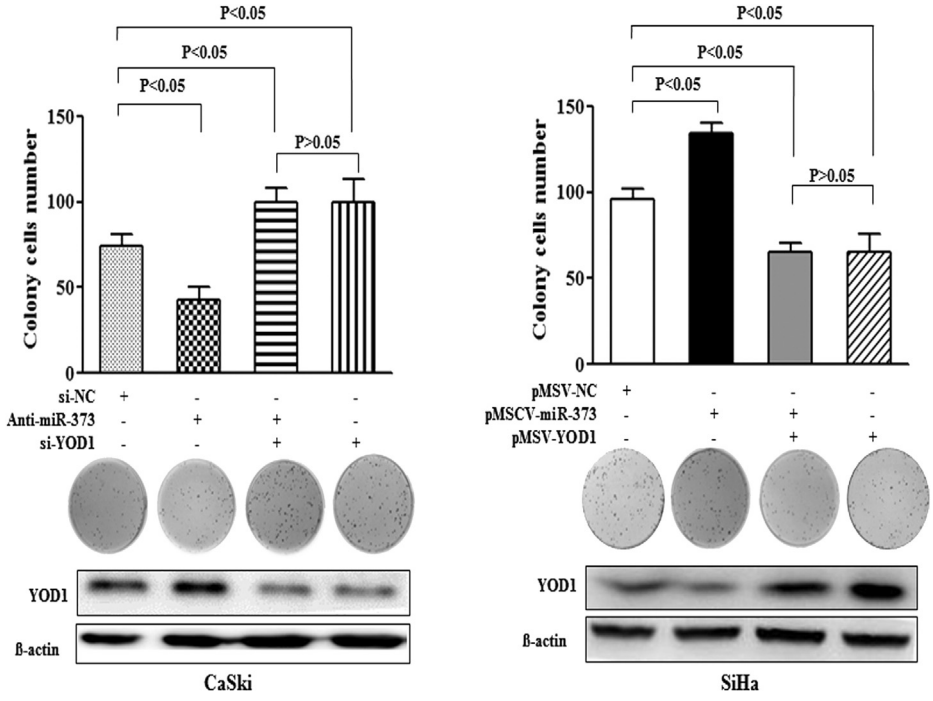

Fig. 3. miR-373 promotes cervical cancer cell growth via downregulation of YOD1 expression. (A) Knockdown of YOD1 by siRNA significantly promoted the proliferation of CaSKi cells; knockdown of miR-373 restored endogenous YOD1 protein expression; and miR-373 silencing could not repress proliferation in YOD1-depleted CaSKi cells. (B) Overexpression of miR-373 by pMSCV-miR-373 significantly promoted the proliferation of SiHa cells; overexpression of miR-373 suppressed endogenous YOD1 protein expression; and overexpression of YOD1 could significantly abrogate miR-373-induced cell growth in SiHa cells.

with Cdc48, to regulate the processing of the endoplasmic reticulum (ER) membrane embedded transcription factor Spt23 [18]. Ernst and colleagues showed that YOD1 is a constituent of a multiprotein complex with p97 as its nucleus that drives the dislocation of ER [19]. p97 (also called CDC48 in yeast) has been shown to possess numerous activities and participate in many biological processes, some of which are important for cell homeostasis. There is also increasing evidence suggesting that p97 and/or some of its adaptors play a role in cancer [20]. Alexandru et al. showed that depletion of p97 leads to accumulation of endogenous HIF1α and increased expression of a HIF1α target gene [21]. When looking at the data as a whole, there is very little evidence linking YOD1 to proliferation control and cancer. Moreover, the mechanism of underexpression of YOD1 in cancer has not yet been elucidated. In the present study, it was confirmed that miR-373 directly targets YOD1 by binding its 3′-UTR. Therefore, upregulation of miR-373 may contribute to the decreased expression of YOD1 in the post-transcription level and in turn promote carcinogenesis and progression of cervical cancer. In the future, more direct proof is needed to find out the direct role played by YOD1 in controlling tumor cell proliferation in cancer cells.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Transparency document

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Appendix A. Supplementary data

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