Open Access

Article Type: Research Article

Volume 2 Issue 2 - 2024

SCIBASE Journals

SciBase Oncology

Interferon-Induced Transmembrane Protein 2 Promotes the Invasion of Oral Squamous Cell Carcinoma by Upregulating Matrix Metalloproteinases

Yang Zhou[1]; Zhihui Chen[2]*

[1]Department of Stomatology, PLA Joint Logistics Support Unit 904 Hospital, Wuxi 214000, China.

[2]Department of Stomatology, Wuxi Fifth People's Hospital, Wuxi 214000, China.

Corresponding Author: Zhihui Chen

Department of Stomatology, Wuxi Fifth People's Hospital, Wuxi 214000, China.

Email: 13771133730@163.com

Article Information

Received: Aug 02, 2024

Accepted: Sep 20, 2024

Published: Sep 27, 2024

SciBase Oncology - scibasejournals.org

Citation: Zhou Y, Chen Z. Interferon-Induced Transmembrane Protein 2 Promotes the Invasion of Oral Squamous Cell Carcinoma by Upregulating Matrix Metalloproteinases. SciBase Oncol. 2024; 2(2): 1018.

Abstract

Objective: This study explores the role of interferon-induced transmembrane protein 2 in the oral squamous cell carcinoma invasion, attempting to identify new target for the oral squamous cell carcinoma treatment.

Methods: Oral squamous cell cells (CAL27 and HSC-3) were assigned as control group and IFITM2 knockdown group (transfected with IFITM2 siRNA sequence), or control group and IFITM2 overexpression group (transfected with overexpressed plasmid pVAX1-IFITM2), respectively. The effect of overexpression or knockdown of IFITM2 was verified by western blot and RT-qPCR, and then the wound healing rate or the cell number of migration and invasion were detected by scratch test and transwell assay. Finally, the expression levels of MMP12 and MMP13 genes in CAL27 and HSC-3 with upregulated or downregulated IFITM2 were further detected by RT-qPCR.

Results: Western blot and RT-qPCR showed that the siIFITM2#1 and siIFITM2#2 sequences of IFITM2 in CAL27 and HSC-3 cells had a significant knockdown effect ($p<0.05$). Compared with the control group, the wound healing rate of CAL27 and HSC-3 cells in the IFITM2 knockdown group was significantly decreased ($p<0.05$). The cell number of migration and invasion were also significantly decreased ($p<0.05$). Meantime, the IFITM2 in CAL27 and HSC-3 cells transfected with the overexpression plasmid pVAX1-IFITM2 was significant overexpressed ($p<0.05$). And the wound healing rate of CAL27 and HSC-3 cells in the IFITM2 overexpression group was significantly increased ($p<0.05$). The cell number of migration and invasion were also significantly increased ($p<0.05$). Finally, compared with control cells, MMP12 and MMP13 genes were up-regulated in OSCC cells with overexpressed IFITM2 ($p<0.05$), while MMP12 and MMP13 genes were down-regulated in OSCC cells with knocked-down IFITM2 ($p<0.05$).

Conclusion: IFITM2 promotes OSCC invasion by up-regulating matrix metalloproteinase gene expression, and IFITM2 is expected to be a therapeutic target for OSCC.

Keywords: Head and neck squamous cell carcinoma; Oral squamous cell carcinoma; Interferon induced transmembrane protein; Invasion; Matrix metalloproteinases.

Introduction

Head and neck tumor is the sixth most common malignant tumor in the world, and especially Head and Neck Squamous Cell Carcinoma (HNSCC) is still a difficult problem in clinal treatment. How to improve the diagnosis and treatment effect of HNSCC, and improve the survival rate and quality in the mode of comprehensive treatment, and achieve accurate treatment according to the individual differences of patients is an urgent problem to be solved by scholars at home and abroad, which is of great social significance [1]. The treatment strategy of early patients with HNSCC is mainly simple surgery or radical radiotherapy, and advanced patients are mainly treated by surgical synchronous radiotherapy and chemotherapy. Despite the improvement in diagnostic and treatment strategies, the prognosis of HNSCC is still very poor, with an overall 5-year survival rate of only 20% to 35% [2]. Oral Squamous Cell Carcinoma (OSCC) is the most common malignant tumor of HNSCC, and invasion is one of the bottlenecks in the clinical treatment of OSCC, and exploring new targets that affect OSCC invasion is crucial for its clinical treatment [3,4].

Interferon-Induced Transmembrane Protein 2 (IFITM2) is a member of the IFITM family, which includes at least two other functional proteins, IFITM1 (9e27) and IFITM3 (1e8U). Most studies focus on the antiviral function of IFITM [5,6], however, the role in cancer biology is little known [7]. In recent years, the role of the IFITM family in cancer progression has attracted more and more attention. IFITM1 and IFITM3 have been reported to play an important role in many different types of cancers, including head and neck squamous cell carcinoma, oral squamous cell carcinoma, stomach cancer, prostate cancer, colorectal cancer, breast cancer, etc. [8-13]. However, there is less research on the role of IFITM2 in cancer cells. According to the literature, it is reported that IFITM2 is highly expressed in some types of cancers, including colon cancer, gastric cancer and renal clear cell carcinoma [14-16]. However, there is no research has been reported on the role of IFITM2 in oral squamous cell carcinoma.

Study reported that the overexpression of IFITM1 promotes the invasion and migration of HNSCC cells in vitro, and IFITM1 can affect the radiotherapy effect of oral cancer [9]. The high expression of IFITM1 and IFITM3 is also associated with poor prognosis of HNSCC [11]. It can be seen that the interferon induced transmembrane protein family plays an important role in the progression of head and neck malignant tumors, and is expected to become a target for the diagnosis and treatment of head and neck malignant tumors. However, the role of IFITM2, another member of the IFITM family, in OSCC or even HNSCC has not been reported so far. Therefore, it is necessary to explore the role of IFITM2 in OSCC to provide new targets for the clinical diagnosis and treatment of OSCC.

Matrix Metalloproteinases (MMP) are involved in some aspects of tumor metastasis, such as tumor-induced angiogenesis, tumor invasion and the establishment of metastatic lesions at secondary sites, which has attracted widespread attention [17]. Research reports indicate that MMPs also play an important regulatory role in the progression of OSCC [18-22]. MMPs can not only regulate OSCC proliferation and angiogenesis, but also promote OSCC invasion and metastasis, and also affect OSCC prognosis [23]. More important, it is reported that MMP12 and MMP13 are significantly increased in HNSCC cells with IFITM1 overexpressed, which is closely related to HNSCC invasion [19].

This study aims to identify the role of IFITM2 in OSCC invasion by constructing OSCC cells overexpressing and knocking down IFITM2, and then elucidate the relationship between IFITM2's influence on OSCC invasion and matrix metalloproteinase expression, providing a research basis for exploring new clinical targets for OSCC treatment.

Materials and methods

Cells and reagents

Human tongue squamous carcinoma cell CAL27 and human oral squamous carcinoma cell HSC-3 are from American Model Culture Institute (ATCC, Manassas, VA). DMEM and fetal bovine serum medium are from Hyclone, and glutamine and penicillin streptomycin is from Gibco (Carlsbad, CA). The IFITM2 siRNAs are from Beijing Tsingke Biotechnology Co., Ltd, and the siRNA sequences are #1 AGCAGGAAGTGGCTATGCT, #2 TGACCATTCTGCTCATCAT, #3 GCCCTGATTTTGGGCATCT. siRNA transfection reagent is from Invitrogen. The plasmid pVAX1-IFITM2 was synthesized by Beijing Tsingke Biotechnology Co., Ltd. Co., Ltd., and human IFITM2 sequence is from PubMed, with enzyme cutting site NheI-BamHI. Plasmid transfection reagent Lipo2000 is from Invitrogen. The protease phosphatase inhibitor is from Beijing Solarbio Science & Technology Co., Ltd, and the BCA protein quantification Kit is from Beyotime Biotechnology. The anti-IFITM2 and anti-GAPDH antibody purchased from Proteintech, and the secondary antibody purchased form ZSGB-Bio. The reagent for qPCR, including Trizol, reverse transcription kit, qPCR mix are from TaKaRa. qPCR primers were synthesized by Beijing Tsingke Biotechnology Co., Ltd., China. 0.1% crystalline purple staining purchased from Solarbio.

Cell culture

The culture medium of human tongue squamous carcinoma cells CAL27 and human oral squamous cancer cells HSC-3 cells is the basic culture medium high-sugar DMEM plus 10% fetal bovine serum, and 1% glutamine and penicillin streptomycin are added. The cells grow at 37°C and 5% CO_2 conditions. The cells were set to transfection siRNA control group, and the experimental group was transfected three sequences of IFITM2-siRNA respectively; or the control group was set as transfected carrier plasmid pVAX1 and the experimental group was transfected plasmid pVAX1-IFITM2 expressing over-IFITM2.

Cell transfection

Cultivate human tongue squamous cell carcinoma cell line CAL27 and human oral squamous cell carcinoma cell line HSC-3, and after inoculation, transfect the siRNA sequence of IFITM2 or over-IFITM2 plasmid pVAX1-IFITM2. The specific steps of transfection: 10^5 cells of each type cells were seeded into a 12 well plate, totaling 4 wells. On the second day, the control and siRNA sequences were transfected separately. According to the siRNA transfection reagent manual, for a 12 well plate, dilute 4 ul of transfection reagent and 30 nM siRNA with 100 µl of serum-free medium, and then mix at 37℃ for 15 minutes. After changing the culture medium for inoculating cells, drip the incubated mixture separately. According to the instructions of Lipo2000 transfection reagent, 10^5 cells were seeded into a 12 well plate for a total of 2 wells. On the second day, plasmids pVAX1 and pVAX1-IFITM2 were transfected separately, with 2.5 µl of transfection reagent and 1.25 µg of plasmid diluted with 62.5 µl of serum-free medium. After mixing, incubate at 37℃ for 15 minutes. After replacing the inoculated cell culture medium, drip the incubated mixture separately, and replace with

fresh culture medium again after 8 hours.

Western blot

Cultivate human tongue squamous cell carcinoma cell line CAL27 and human oral squamous cell carcinoma cell line HSC-3, and transfect with siRNA sequence of IFITM2 or plasmid pVAX1-IFITM2 overexpressing IFITM2 after inoculation. 72 hours later, extract total cellular protein using RAPI reagent and add phosphatase inhibitor; after collecting the protein, measure the protein concentration using the BCA protein quantification kit, and then add sample buffer for protein denaturation. After denaturation, SDS-PAGE gel electrophoresis was carried out: the electrophoresis voltage was 80V to 120V; then transfer membrane after the electrophoresis with the condition was 350mA, lasting for 1 hour; then the membrane was placed in 5% skimmed milk powder at room temperature and closed for 1 hour; and the rabbit anti human IFITM2 antibody or mouse anti human GAPDH antibody was incubated, diluted 1:1000, 4 ℃ overnight; The next day, PBST was cleaned and incubated with a 1:5000 dilution of secondary antibody. Then, ECL luminescent solution was exposed and photographed using a chemiluminescence analyzer.

Real time fluorescence quantitative reverse transcription PCR (RT-qPCR)

Cultivate human tongue squamous cell carcinoma cell line CAL27 and human oral squamous cell carcinoma cell line HSC-3, and transfect them with siRNA sequence of IFITM2 or plasmid pVAX1-IFITM2 overexpressing IFITM2 after inoculation. After 36 hours, total RNA was extracted from the cells using Trizol, and cDNA was synthesized using a reverse transcription kit, followed by fluorescence quantitative PCR. The qPCR primers were synthesized by Beijing Tsingke Biotechnology Co., Ltd. The sequences are shown in Table 1.

Table 1: qPCR primers sequences.

Genes	Forward (5′-3′)	Reverse (5′-3′)
IFITM2	GGCTTCATAGCATTCGCGTACTC	AGATGTTCAGGCACTTGGCGGT
MMP12	GATGCTGTCACTACCGTGGGAA	CAATGCCAGATGGCAAGGTTGG
MMP13	CCTTGATGCCATTACCAGTCTCC	AAACAGCTCCGCATCAACCTGC
GAPDH	GAGTCAACGGATTTGGTCGT	GACAAGCTTCCCGTTCTCAG

Scratch test

Human tongue squamous carcinoma cells CAL27 with IFITM2 knock low or overexpression and human oral squamous carcinoma cells HSC-3 are inoculated in a 12-hole plate with a cross-marking line on the back. When the cell area reaches 80% or more, make an artificial wound with the tip of a 10 μl pipette, then change the liquid, and take photos with an inverted microscope. After 24 hours, observe the wound healing and take photos in the same position, and then calculate the wound healing rate through Image J software.

Transwell assay

Transwell migration was performed by inoculating 5×10^3 tumor cells (human tongue squamous carcinoma cell CAL27 and human oral squamous carcinoma cell HSC-3) into 200 μl serum-free DMEM medium in the upper chamber by using an 8 μM pore polycarbonate membrane filter. For invasion assay, 10^4 tumor cells were added to the 200 μl serum-free DMEM medium, and the matrigel was pre-flattened on insert for 4 hours. After incubation for 24 hours, fix the upper insert with 4% polyformaldehyde for 15 minutes and dye it with 0.1% crystalline purple at room temperature for 15 minutes. Then count the number of cells in three different fields under the insert.

Statistic analysis

All histograms use GraphPad Prism9.0,drawing and statistical analysis, and all quantitative data are expressed in the average ± standard deviation, the t test is compared in two groups, and $p<0.05$ is considered to have statistical significance.

Results

Silencing the IFITM2 expression inhibits the invasion of OSCC cells

WB detects the knock-down effect of IFITM2 in CAL 27 and HSC-3 cells, and found that the si#1 and si#2 sequences of IFITM2 have a significant knock-down effect (Figure 1a). (Figure 1b) shows that qPCR detection also found the si#1 and si#2 sequences of IFITM2 have a significant knock-down effect in CAL 27 and HSC-3 cells. CAL27 (siIFITM2#1 vs control $p<0.0001$, $t=19.67$; siIFITM2#2 vs control $p=0.0043$, $t=5.841$), HSC-3 (siIFITM2#1 vs control $p=0.0168$, $t=3.948$; siIFITM2#2 vs control $p=0.0412$, $t=2.969$). The calculation results show that the difference is statistically significant.

The scratch experiment detects the change of cell healing ability of CAL27 and HSC-3 cells after knocking down IFITM2. The results in Figure 1c show that the healing ability of cells is significantly weakened after knocking down the OSCC cell IFITM2. (Figure 1c) is a representative picture of scratch experimental detection. (Figure 1d) shows Image J's analysis of the wound healing rate calculated by three different fields. The histogram is the average value of the three fields, the bar is the standard deviation, with CAL27 ($p=0.0066$, $t=5.172$), HSC-3 ($p=0.0275$, $t=3.391$), and the difference has statistical significance.

Similarly, (Figure 1e) is the representative picture of the significant weakening of the migration and invasion ability of CAL27 and HSC-3 cells after Transwell migration and invasion experiment detection knocking down IFITM2. (Figure 1f) shows the number of cells calculated from three different visual fields, and the histogram is three visions. The average value of the cell numbers, bar is the standard deviation, and CAL27 cell migration (siIFITM2#1 vs control $p=0.001$, $t=8.549$; siIFITM2#2 vs control $p=0.0006$, $t=9.\ 971$), invasion (siIFITM2#1 vs control $p=0.0013$, $t=8.081$; siIFITM2#2 vs control $p<0.0001$, $t=17.43$), and HSC-3 cell migration (siI FITM2#1 vs control $p=0.0002$, $t=12.76$; siIFITM2#2 vs control $p=0.0038$, $t=6.023$), invasion (siIFITM2#1 vs control $P=0.0002$, $t=12.55$; siIFITM2#2 vs control $p=0.0005$, $t=10.16$), and the difference is statistically significant.

Collectively, silencing IFITM2 can inhibit the invasion ability of human oral squamous cell carcinoma cells.

Overexpressed IFITM2 promotes the invasion of OSCC cells

(Figure 2a) shows that WB detection of transfected recombinant plasmid pVAX1-IFITM2 can significantly improve the expression of IFITM2 protein in CAL27 and HSC-3 cells. (Figure 2b) also shows that transfected recombinant plasmid pVAX1-IFITM2 can significantly improve the expression of IFITM2 mRNA in CAL27 and HSC-3 cells, with CAL27 ($p<0.0001$, $t=17.98$), HSC-3 ($p=0.0028$, $t=6.556$), and the difference is statistically significant.

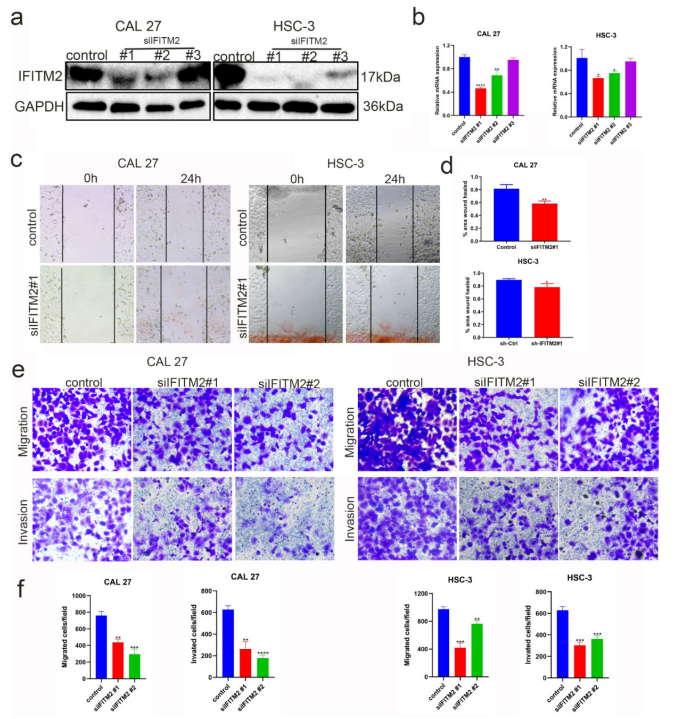

Figure 1: Knocking down IFITM2 inhibits OSCC cell invasion. **(a)** The expression of IFITM2 protein was detected by WB after transfection of IFITM2 siRNA sequence in CAL27 and HSC-3 cells; **(b)** The mRNA expression of IFITM2 was detected by qPCR after transfection of IFITM2 siRNA sequence in CAL27 and HSC-3 cells; **(c)** Representative pictures of cell wound healing changes after IFITM2 knock-downed in CAL.27 and HSC-3 cells were detected by scratch test; **(d)** Image J analyzed and calculated the wound healing rate of CAL27 and HSC-3 cells; **(e)** Transwell migration and invasion assay detected the representative pictures of changes in cell invasion status after IFITM2 knocked down in CAL27 and HSC-3 cells; **(f)** The number of migrating and invading cells of CAL27 and HSC-3 under three different visual fields was calculated.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

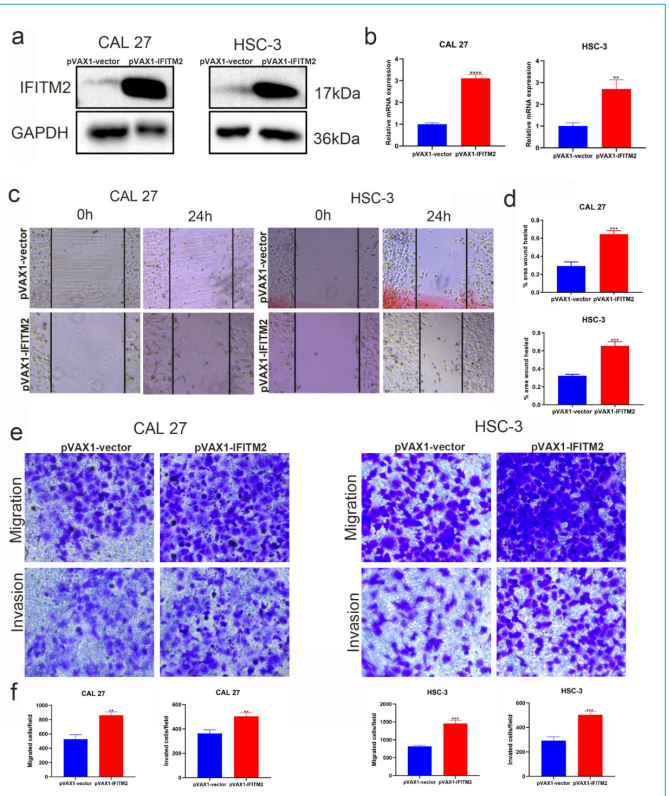

Figure 2: Overexpressed IFITM2 promotes OSCC cell invasion. **(a)** The protein changes of IFITM2 in CAL27 and HSC-3 cells were detected by WB; **(b)** The mRNA changes of IFITM2 in CAL27 and HSC-3 cells were detected by qPCR; **(c)** Representative pictures of wound healing changes of CAL27 and HSC-3 cells after the IFITM2over-expression was detected by scratch test; **(d)** Image J analyzed and calculated the wound healing rate of CAL27 and HSC-3cells; **(e)** Transwell migration and invasion assay to detect the changes of invasion status of CAL27 and HSC-3 cells after high expression of IFITM2; **(f)** The number of migrating and invading cells of CAL27 and HSC-3 under three different visual fields was calculated.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

The scratch experiment shown in (Figure 2c) detected a significant improvement in the healing ability of CAL27 and HSC-3 cells after overexpressing IFITM2. (Figure 2d) is the wound healing rate calculated by three different fields shown in the ImageJ analysis. The histogram is the average value of the three visions, the bar is the standard deviation, and CAL27 cells (p=0.0005, T=10.12), HSC-3 (p=0.0003, t=11.39), the difference is statistically significant.

Similarly, (Figure 2e) shows representative image changes in the invasion status of CAL27 and HSC-3 cells after detecting high expression of IFITM2 in Transwell migration and invasion experiments. (Figure 2f) shows the number of cells calculated by three different fields of views, the bar chart is the average value of the cell numbers in the three fields, bar is the standard deviation, and CAL27 cell migration (p=0.0019, t=7.25), invasion (p=0.0042, t=5.87), and HSC- 3 Cell migration (p=0.0003, t=11.76), invasion (p=0.0009, t=8.791), and the difference is statistically significant.

In conclusion, consistent with the (Figure 1) results, the regulation of IFITM2 can affect the invasion ability of human oral squamous cell carcinoma cells.

Regulation of IFITM2 expression affects the expression of matrix metalloproteinase in OSCC cells

The results are shown in (Figure 3a) qPCR detected a significant increase in the mRNA expression of MMP12 and MMP13 in CAL27 cells with high expression of IFITM2. MMP12 (p=0.0012, t=8.266), MMP13 (p=0.049, t=5.644), the difference is statistically significant. As shown in (Figure 3b), qPCR detects MMP12 and MMP13 in HSC-3 cells with high expression of IFITM2. MMP12 (p=<0.0001, t=38.77), MMP13 (p=0.0006, t=9.707), and the difference is statistically significant.

Similarly, (Figure 3c) shows that mRNA expression of MMP12 and MMP13 was significantly reduced in CAL27 cells with knockdown of IFITM2. MMP12 (siIFITM2#1 vs control p=0.0343, t=3.157; siIFITM2#2 vs control p=0.0101, t=4.596) and MMP13 (siIFITM2#1 vs control p=0.0085, t=4.824; siIFITM2#2 vs control p=0.0392, t=3.02) in CAL27 cells, the difference was statistically significant. And the mRNA expression of MMP12 and MMP13 in HSC-3 cells with IFITM2 knockdown shown in (Figure 3d) was also significantly reduced, and MMP12 (siIFITM2#1 vs control p=0.0006, t=9.89; siIFITM2#2 vs control p=0.0016, t=7.624), MMP13 (siIFITM2#1 vs control p=0.007, t=5.101; siIFITM2#2 vs control p=0.0475, t=2.827), the difference was statistically significant.

Collectively, IFITM2's role to promote oral squamous cell carcinoma invasion is also related to the expression of MMP-related genes.

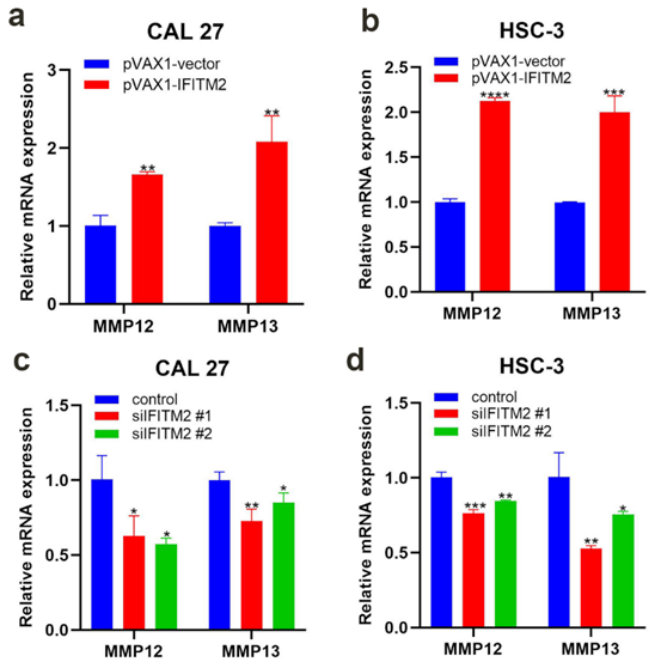

Figure 3: IFITM2 regulates matrix metalloproteinase gene expression. **(a)** qPCR was used to detect the effect of upregulated IFITM2 gene expression on the mRNA expression of MMP12 and MMP13 in CAL27 cells; **(b)** qPCR was used to detect the effect on up-regulated IFITM2 gene expression on MMP12 and MMP13 mRNA expression in HSC-3 cells; **(c)** qPCR was used to detect the effect of down-regulated IFITM2 gene expression on the mRNA expression of MMP12 and MMP13 in CAL27cells; **(d)** The effect of down-regulated IFITM2 gene expression on the expression of MMP12 and MP13 in H$C-3 cells was detected by qPCR.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

Discussion and conclusion

The IFITM family, which includes IFITM1, IFITM2, and IFITM3, has been reported to be implicated in different types of cancer progression: IFITM1 promotes tumor proliferation by regulating the JAK/STAT pathway in cancer [10]; IFITM1 also affects the Wnt/β-catenin pathway to promote Epithelial-Mesenchymal Transition (EMT) in cancer [7]. IFITM3 regulates hepatocellular carcinoma progression through PI3K/AKT/mTOR pathway [24]. And earlier studies have shown that IFITM2 exerts a role as a pro-apoptotic gene in a p53-independent manner, although it is overexpressed in colon cancer [14]. However, IFITM2 also plays an oncogenic role in various cancers: IGF1/IGF1R/STAT3 signaling induces IFITM2 to promote gastric cancer growth and metastasis [15], and IFITM2 promotes cancer progression by inducing malignant features and lymphatic metastases in renal Clear Cell Carcinoma (ccRCC) [16].

Oral malignant tumors are common malignant tumors in the world, and about 90% of oral cancer patients are Oral Squamous Cell Carcinomas (OSCC), which seriously threatens human health. Despite the fact that in recent years in the prevention of OSCC, great progress has been made in diagnosis and treatment, but many patients still die due to metastasis and recurrence, and the search for the invasion mechanism and therapeutic targets of oral squamous cell carcinoma is helpful for early intervention of tumor progression [25]. Studies have found that IFITM1 is overexpressed in head and neck squamous cell carcinoma, and high expression of IFITM1 or IFITM3 is associated with poor prognosis of HNSCC [11], and IFITM1 can also affect the radiotherapy effect of oral cancer [9]. Thus, clarifying the role of the IFITM family in OSCC is of great significance for identifying the IFITM family as a target for OSCC.

This study focuses on IFITM2, a member of the IFITM family, and the role of IFITM2 in cancer progression compared to IFITM1 and IFITM3 has rarely been reported, especially in OSCC. By regulating the expression of IFITM2 in OSCC cells, the effect of IFITM2 on the invasion ability of OSCC cells was detected by cell invasion assays (scratch assay and Transwell assay) to clarify the importance of IFITM2 in OSCC invasion. More importantly, it was also found that IFITM2 regulates the expression of Matrix Metalloproteinase (MMP) genes. Stromal metalloproteinases have been reported to be involved in the metastasis of many different tumor types [17], including pancreatic cancer [26], head and neck squamous cell carcinoma [27], and even oral squamous cell carcinoma [28]. Additionally, it has been reported that the expression of several matrix metalloproteinases in IFITM1-overexpressing HNSCC cells is significantly up-regulated, which is closely related to the invasiveness of HNSCC [19]. Therefore, the reason why IFITM2 promotes OSCC invasion is highly likely due to its regulation of the expression of matrix metalloproteinase genes MMP12 and MPP13.

However, it has been reported in the literature that the IFITM family may regulate cancer progression through a variety of pathways, including Asona et al., which found that IFITM1 promotes breast cancer cell proliferation by inhibiting p21 transcription, expression, and nuclear localization mediated by the JAK/STAT pathway [10]; Liu et al. found that IFITM3 exerts an oncogenic role in advanced prostate cancer progression through a novel TGF-β-Smads-MAPK pathway [13]; Hou et al. demonstrated that IFITM3 regulates cellular progression in Hepatocellular Carcinoma (HCC) through the PI3K/AKT/mTOR signaling pathway [24]; Gan et al. proposed that IFITM3 regulates the CCND1-CDK4/6-pRB axis to mediate OSCC cell growth [12]. In addition, both IFITM1 and IFITM3 upregulate the expression of several matrix metalloproteinases MMPs to promote cell migration and invasion by stimulating extracellular matrix remodeling, such as head and neck cancer [19] or colorectal cancer [29]. So, is the key mechanism by which IFITM2 promotes OSCC invasion affect the expression of related matrix metalloproteinases? Or is it also involved in other pathways that promote cancer progression? This needs to be further explored.

In summary, our results innovatively found the important role of IFITM2 in OSCC invasion, but the current data are not sufficient, and the effect of IFITM2 on OSCC invasion needs to be further confirmed in vivo animals or clinical tissues, providing a more favorable theoretical basis for further exploring IFITM2 as a therapeutic target for OSCC.

Declarations

Conflict of interest statement: The authors declare that they have no competing interests.

Funding: Not applicable.

Acknowledgements: Not applicable.

References

1. Kawada T, Takahashi H, Sakakura K, et al. Circulating tumor cells in patients with head and neck squamous cell carcinoma: Feasibility of detection and quantitation [J]. Head & neck. 2017; 39(11): 2180-2186.

2. Wong KCW, Johnson D, Hui EP, et al. Opportunities and challenges in combining immunotherapy and radiotherapy in head and neck cancers [J]. Cancer Treat Rev. 2022; 105: 102361.

3. Kaminagakura E, Tango TN, Cruz Perez D, et al. Oral squamous cell carcinoma outcome in adolescent/young adult: systematic review and meta-analysis [J]. Head Neck. 2022; 44(2): 548-561.

4. Nijakowski K, Gruszczynski D, Kopala D, et al. Salivary metabolomics for oral squsmous cell carcinoma diagnosis: A systematic review [J]. Metabolites. 2022; 12(4): 294.

5. J Lu, Q Pan, L Rong, W He, SL Liu, et al. The IFITM proteins inhibit HIV-1 infection, J. Virol. 2011; 85(5): 2126e2137.

6. AL Brass, IC Huang, Y Benita, SP John, MN Krishnan, et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus, Cell. 2009; 139(7): 1243e1254.

7. P Andreu, S Colnot, C Godard, P Laurent-Puig, D Lamarque, et al. Identification of the IFITM family as a new molecular marker in human colorectal tumors, Cancer Res. 2006; 66(4): 1949e1955.

8. F Yu, D Xie, SS Ng, CT Lum, MY Cai, et al. IFITM1 promotes the metastasis of human colorectal cancer via CAV-1, Cancer Lett. 2015; 368(1): 135e143.

9. Yang J, Li L, Xi Y, et al. Combination of IFITM1 knockdown and radiotherapy inhibits the growth of oral cancer. Cancer Sci. 2018; 109: 3115-3128.

10. Lui AJ, Geanes ES, Ogony J, et al. IFITM1 suppression blocks proliferation and invasion of aromatase inhibitor-resistant breast cancer in vivo by JAK/STAT-mediated induction of p21. Cancer Lett. 2017; 399: 29-43.

11. Li H, Yang LL, Wu CC, et al. Expression and Prognostic Value of IFITM1 and IFITM3 in Head and Neck Squamous Cell Carcinoma. Am. J. Clin. Pathol. 2020; 153: 618-629.

12. Gan CP, Sam KK, Yee PS, et al. IFITM3 knockdown reduces the expression of CCND1 and CDK4 and suppresses the growth of oral squamous cell carcinoma cells. Cell. Oncol. 2019; 42: 477-490.

13. Liu X, Chen L, Fan Y, et al. IFITM3 promotes bone metastasis of prostate cancer cells by mediating activation of the TGF-beta signaling pathway. Cell Death Dis. 2019; 10: 517.

14. V Daniel-Carmi, E Makovitzki-Avraham, EM Reuven, I Goldstein, N Zilkha, et al. The human 1-8D gene (IFITM2) is a novel p53 independent pro-apoptotic gene, Int. J. Cancer. 2009; 125(12): 2810e2819.

15. Xu L, Zhou R, Yuan L, et al. IGF1/IGF1R/STAT3 signaling-inducible IFITM2 promotes gastric cancer growth and metastasis [J]. Cancer Letters. 2017; 393: 76-85.

16. Yang N, et al. Predicative value of IFITM2 in renal clear cell carcinoma: IFITM2 is associated with lymphatic metastasis and poor clinical outcome. Biochem. Biophys. Res. Commun. 2021; 534: 157-164.

17. Deryugina EI, Quigley JP. Matrix metalloproteinases and tumor metastasis. Cancer Metastasis Rev. 2006; 25: 9-34.

18. Chung RJ. Oral Cancer Theranostic Application of FeAu Bimetallic Nanoparticles Conjugated with MMP-1 Antibody [J].Nanomaterials. 2021; 12.

19. Wei Liting, Zhang Hao, He Li, et al. Effect of berberine hydrochloride on proliferation, migration and invasion of human oral squamous cell carcinoma cells. Journal of Clinical Stomatology. 2021; 37(08): 455-459.

20. Miguel AFP, Mello FW, Melo G, Rivero ERC. Association between immunohistochemical expression of matrix metalloproteinases and metastasis in oral squamous cell carcinoma: Systematic review and meta-analysis. Head Neck. 2020; 42(3): 569-584.

21. Celentano A, Yap T, Paolini R, et al. Inhibition of matrix metalloproteinase-2 modulates malignant behaviour of oral squamous cell carcinoma cells [J]. Journal of oral pathology and medicine: Official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 2021; 3: 50.

22. Choudhry N, Sarmad S, Waheed NUA, Gondal AJ. Estimation of serum matrix metalloproteinases among patients of oral squamous cell carcinoma. Pak J Med Sci. 2019; 35(1): 252-256.

23. Deraz EM, Kudo Y, Yoshida M, et al. MMP-10/stromelysin-2 promotes invasion of head and neck cancer. Plos One. 2011; 6: e25438.

24. Hou Y, Wang S, Gao M, Chang J, Sun J, et al. Interferon-Induced Transmembrane Protein 3 Expression Upregulation Is Involved in Progression of Hepatocellular Carcinoma. Biomed Res Int. 2021; 5612138.

25. Singh S, Singh AK. Porphyromonas gingivalis in oral squamous cell carcinoma: Are view (J). MicrobesInfect. 2022; 24(3): 104925.

26. Wang Jianqiang, Qiu Aiyan, Zhang Haiwen, et al. Inhibition of migration and invasion of human pancreatic cancer cells by matrix metalloproteinase inhibitors. Modern Oncology Medicine. 2019; 31(22): 4153-4157.

27. The expression level of matrix metalloproteinase-1 in head and neck squamous cell carcinoma and the regulation of micrornas in bioinformatics. Journal of Shanxi Medicine. 2019; 52(14): 1043-1049.

28. Liu Wanying, Jin Suhan, Tang Jing, et al. The role of matrix metalloproteinases in the pathogenesis of oral diseases. Journal of Clinical Stomatology. 2019; 39(10): 630-633.

29. He JD, Luo HL, Li J, et al. Influences of the interferon induced transmembrane protein 1 on the proliferation, invasion, and metastasis of the colorectal cancer SW480 cell lines. Chinese Med. J Peking. 2012; 125: 517-522.