miR-29a-3p enhances the radiosensitivity of oral squamous cell carcinoma cells by inhibiting ADAM12

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Oral squamous cell carcinoma (OSCC) is the most common malignant tumor in the head and neck, and radiotherapy is the main approach for this disease, while irradiation resistance is a huge challenge that influences radiosensitivity. This study aims to determine the role and function of miR-29a-3p and ADAM12 in the radiosensitivity of OSCC cells. The expression pattern of ADAM12 in OSCC cells was searched in TCGA database. The binding of miR-29a-3p and ADAM12 was predicted by Starbase and verified using dual luciferase reporter gene assay. The RNA or protein expressions of miR-29a-3p and ADAM12 were measured by RT-qPCR or western blot. OSCC cell lines were treated by various γ-ray irradiation dosages before the alteration on miR-29a-3p expression and on the cell viability, proliferation, migration and cell apoptosis was detected. ADAM12 was highly expressed in OSCC cells, whose expression in resistant cells was positively correlated with irradiation dosage. Overexpression of ADAM12 in OSCC cells lead to increased cell proliferation and migration ability as well as inhibited cell apoptosis. miRNAs potentially binding ADAM12 in PITA, microT, miRmap and targetscan were screened, among which miR-29a-3p had the maximum differential expression levels in OSCC cells determined by RT-qPCR. Overexpression of miR-29a-3p resulted in suppressed cell viability, proliferation, migration ability and increased cell apoptosis, while this expression pattern can be partially counteracted by ADAM12 overexpression in OSCC cells. miR-29a-3p through targeting and inhibiting ADAM12 enhances the radiosensitivity of OSCC cells.

Key words: miR-29a; ADAM12; oral squamous cell carcinoma; radio-resistance; cell viability

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Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies and accounts for the majority of cases in head and neck squamous cell carcinomas (HNSCCs). The OSCC-related mortality ranks the top eight of cancer-related death with an increasing incidence of more than 300,000 new cases being newly diagnosed each year. The prognosis for this disease is extremely poor and less than half of OSCC patients can survive the first 5 years, which can be partially ascribed into metastasis and resistance. The treatment options of OSCC include surgical resection for locally OSCC and adjuvant treatment (chemotherapy or radiotherapy) for advanced OSCC. Especially for patients in stage III-IV, adjuvant thermontherapy is the most effective choice, but despite the advances in recent years, the prognosis for patients in advanced stage is still far from satisfactory. The major obstacle is chemo-resistance. Therefore, decreasing chemotherapy or radiotherapy resistance is of great importance for improving the overall survival of OSCC patients.

ADAM12 is a protein which was involved in cell adhesion and whose expression is showed to be lowly expressed in radio-resistant human nasopharyngeal carcinoma tissues. The alternation of miR-29a-3p expression in a pro-fibrosis model indicates a higher risk for radiation therapy, suggesting miR-29a-3p may implicated in biological tumor progression, migration, invasion and apoptosis. miRNAs have been well proved for their implication in cell proliferation, invasion, migration and apoptosis. The dysregulated expression of multiple miRNAs has been reported in OSCC, indicating miRs have certain role to play in the progression of OSCC. miR-29a-3p, included in OSCC-derived exosomes (OSCC-Exo) was showed to promote M2 subtype macrophage polarization through regulating SOCS1/STAT6 signal pathway. In addition to that, miR-29a-3p, as a tumor suppressor, was found to be upregulated expression in OSCC-derived cell lines and was associated with TNM classification in OSCC patients. Nevertheless, no current data supported the implication of ADAM12 in chemoresistance of OSCC. After searching several databases to identify the possible upstream targets of ADAM12, we identified five microRNAs (miRNAs or miRs), including hsa-miR-29a-3p, hsa-miR-29b-3p, hsa-miR-217, hsa-miR-29c-3p and hsa-miR-582-5p, among which miR-29a-3p was finally selected.

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Method and Materials

Cell culture, transfection and radiation

Normal human oral keratinocytes (NHOK) and OSCC cell lines (HSC2, HSC4 and SCC4) were purchased from ATCC and cultured in Roswell Park Memorial Institute 1640 (RPMI 1640, Gibco, New York, NY, USA) which contains 10% fetal bovine serum (FBS, 16140071, Gibco) + 1% double antibiotics (15240062, 100×, Gibco) in an incubator at 37°C with 5% CO₂.
Cells (1×10⁶) were washed in pre-cold PBS for twice and suspended in 1 × Annexin buffer before incubation with 5 μL Annexin-V-FITC (Becton Dickinson) at room temperature for 10 min without light exposure. Then cells were washed in pre-cold PBS and suspended in 300 μL 1 × Annexin. Cell apoptosis rate was calculated using flow cytometry (Guava easyCyte HT from Millipore, Burlington, MA, USA).

Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

miR-29a-3p Oligod (T) specific RT primers were designed. Cells were dissolved in 1 mL Trizol (Thermo Fisher Scientific, Waltham, MA, USA) to extract the total RNA based on instructions. RNA samples in which the miR-29a-3p expression was detected were treated with 3’ poly-A tail. RNAs were reversed transcript into cDNA using M-MLV reverse transcriptase (D7160L, Beyotime, Shanghai, China) and random primers. The PCR reaction system and reaction conditions were prepared based on the instructions of Premix Ex Taq™II kit (Takara, Dalian, China). ABI7500 quantitative PCR apparatus (Applied Biosystems, Shanghai, China) was used for RT-PCR with U6 as internal control of miRNA and GAPDH of mRNA. Data were analyzed using 2-ΔΔCt method: ΔΔCt = [Ct(target gene) - Ct(internal gene)]experimental group - [Ct(target gene) - Ct(internal gene)]control group. The primers for gene are listed in Table 1.

Western blot

Cells were treated by lysis buffer, in which the concentration of total protein was measured using bicinchoninic acid (BCA) kit (23227, Thermo Fisher Scientific). Then proteins were diluted with 5 × sample buffer and separated in 12% separating gel for 90 min before being blocked in PBS blocking buffer with 5% (w / v) skimmed milk powder at room temperature for 1 h. After that, cells were incubated with primary antibody of ADAM12 (1:500, ab223476, Abcam, Cambridge, UK) and GAPDH (1:500, ab9485, Cambridge, UK) at 4°C for overnight. The membranes were washed and incubated with secondary antibody (1: 500, ab114610, Abcam) at room temperature for 1 h. The images were photographed and saved at BioSpectrum Imaging System (UVP, Upland, CA, USA).

Dual luciferase reporter gene assay

The potential binding sites between ADAM12 and miR-29a-3p were predicted by TargetScan and the wide and mutant sequences were accordingly designed. The sequence segments were cloned into pGL3-Basic (Promega, Madison, WI, USA) and accordingly named as MT-ADAM12 group and WT-ADAM12 group. MT-

Table 1. Primers of genes for RT-qPCR.

| Name of primer | Sequences (5’-3’) |
|----------------|------------------|
| ADAM12-F       | GCTGACCAGTTCTACAGG |
| ADAM12-R       | GGGGCTTCAGTGATAGA |
| miR-29a-3p-F   | ATTGGCTAAAGTCTAC |
| miR-29a-3p-R   | TGGTGTCGTGGAGTCG |
| U6-F           | CTCGCTTCGGCACACA |
| U6-R           | AACGCTTCGAATTTGCT |
| GAPDH-F        | GTGGCTGGCGCTGAAGG |
| GAPDH-R        | GGGGAGATTCAGTGTGG |

F, forward primer; R, reverse primer.

Figure 1. Elevated ADAM12 expression in radio-resistant OSCC cells. Expression profile of ADAM12 in patients with head and neck squamous cell carcinomas was searched in TCGA database (A). RT-qPCR (B) and Western blot (C) were applied to determine the expression level of ADAM12 in OSCC cell lines (HSC2, HSC4 and SCC4) and NHOK cells. The alternation on ADAM12 expression in HSC2 cell after radiation under 5 Gy, 10 Gy and 20 Gy was determined by RT-qPCR (D) and western blot (E). n=3, *p<0.05; **p<0.01. OSCC, oral squamous cell carcinoma.
ADAM12 or WT-ADAM12 with miR-29a mimic or mimic-NC was transfected into HSC2 cells. Forty-eight hours after transfection, the luciferase activity in each group was detected by luciferase detection kit (RG051S, Beyotime).

**Statistical analysis**

All experiments were performed in triplicates, unless indicated otherwise. SPSS 18.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software Inc.) were used for data analysis. Measurement data were expressed as mean ± SD. Comparisons between two groups were analyzed using t-test while comparisons among multiple groups were determined by One-way analysis of variance with Tukey’s for post hoc analysis. A p-value <0.05 was considered to have significant difference.

**Results**

**Elevated ADAM12 expression in radio-resistant OSCC cells**

Data in TCGA database showed elevated expression of ADAM12 in patients with HNSCC (Figure 1A). Detection on ADAM12 expression in OSCC cell lines (HSC2, HSC4 and SCC4) and NHOK cells showed that OSCC cell lines had higher expression level of ADAM12 than those in NHOK cells (Figure 1 B,C; p<0.01). HSC2 cells were selected for presentation in following experiments.

Once cell confluence reaches 90%, HSC2 cells were treated by radiation of 0 Gy, 5 Gy, 10 Gy and 20 Gy at the frequency of 137...
Cs 0.5 Gy/min. The measurement on ADAM12 expression showed
the expression of ADAM12 in survived cells was increased along
with the increased radiation dose (Figure 1D; p 0.01), indicating
the possible regulatory role of ADAM12 in radio-resistance of
OSCC cells. In this regard, radiation at the dose of 20 Gy was used
for following experiments.

**Knockdown of ADAM12 enhances the radio-sensitivity
of OSCC cells**

ADAM12 knockdown was achieved in HSC2 cells and the
verification on cell transfection efficiency showed that ADAM12
expression was elevated in OE-ADAM12 group compared with
OE-NC group, but decreased in sh-ADAM2 group compared with
sh-NC group (Figure 2 A,B; p<0.01).

After radiation of 20Gy, cells were measured for cell viability,
migration, proliferation and apoptosis. The results showed that
compared with control group, cells in IR group had suppressed cell
viability, proliferation and migration ability as well as increased
apoptosis rate. Compared with IR group, the cell viability, prolif-
eration and migration ability were elevated and cell apoptosis was
suppressed in IR + OE-ADAM12 group, while different expres-
sion pattern was found in IR + sh-ADAM12 group (Figure 2 C-F;
p<0.01). Those results showed that knockdown of ADAM12 could
increase the radio-sensitivity of OSCC cells and overexpression of
ADAM12 can decrease the radio-sensitivity of OSCC cells.

**miR-29a-3p targets and negatively regulates ADAM12**

To explore the miRNA that can regulate ADAM12 in OSCC,
Starbase was used to predict the possible miRNAs binding to
ADAM12. The overlapped miRNAs in PITA, microT, miRmap,
TargetScan were selected by Venn diagram: hsa-miR-29a-3p, hsa-
mir-29b-3p, hsa-miR-217, hsa-miR-29c-3p, hsa-miR-582-5p
(Figure 3A). Then the expressions of those five miRNAs were
detected in OSCC cell lines which showed that miR-29a-3p had
the lowest expression in OSCC cell lines among the above
miRNAs (Figure 3B; p<0.01). Therefore miR-29a-3p was selected
for following experiments and for cell transfection. Then the
expressions of miR-29a-3p in HSC2 cells after different radiation
dosage were measured and the results showed that the expression
levels of miR-29a-3p was decreased along with the increased radi-
ation dosage (Figure 3C; p<0.01), indicating miR-29a-3p was
associated with the radiation resistance of HSC2 cells. The mea-
surement for transfection efficiency showed that compared with
mimic-NC group, miR-29a-3p mimic group had elevated miR-
29a-3p expression, while compared with inhibitor-NC group, miR-
29a-3p inhibitor group had suppressed miR-29a-3p expression
(Figure 3D).

Dual luciferase reporter gene assay was applied to verify the
possible binding of miR-29a-3p with ADAM12 and the binding
sites are designed in Figure 3E. The measurement showed that
compared with co-transfection with mimic-NC, co-transfection of
WT-ADAM12 with miR-29a-3p mimic resulted in decreased
luciferase activity (Figure 3F; p<0.01). No significant difference
was noticed for cells co-transfected with MT-ADAM12 and miR-
29a-3p mimic. Above results showed miR-29a-3 can target
ADAM12.

To determine the regulatory role of miR-29a-3p on ADAM12,
miR-29a-3p overexpression or miR-29a-3p inhibitor was transfect-
ed into HSC2 cells to detect the expression level of ADAM12. Compared with mimic-NC group, miR-29a-3p mimic group had reduced ADAM12 expression, while compared with inhibitor-NC group, miR-29a-3p inhibitor group had elevated expression level of ADAM12 (Figure 3 G,H; p<0.01). Above results showed that miR-29a-3p can negatively target and regulate ADAM12 expression in HSC2 cells.

**miR-29a regulates ADAM12 to enhance the radio-sensitivity of OSCC cells**

To determine whether the regulatory effect of miR-29a-3p in ADAM12 affects the radio-sensitivity of OSCC, HSC2 cells were transfected or co-transfected with miR-29a-3p or ADAM12 related plasmids before the cell biological function was detected. The detection showed that compared with IR group, cells in IR + miR-29a-3p mimic group had suppressed cell viability, proliferation and migration ability in addition to enhanced apoptosis rate, while different expression pattern was found in cells in IR + miR-29a-3p inhibitor group. Compared to IR + miR-29a-3p mimic group, IR + miR-29a-3p mimic + OE-ADAM12 group had enhanced cell viability, proliferation and migration ability, and suppressed cell apoptosis rate, while compared with IR + miR-29a-3p inhibitor group.
group, cells in IR + miR-29a-3p inhibitor + sh-ADAM12 group had decreased cell viability, proliferation and migration ability, and elevated cell apoptosis rate (Figure 4 A-D; p<0.01). Collectively, miR-29a-3p can negatively regulate ADAM12 expression to enhance the radio-sensitivity of OSCC cells.

**Discussion**

Chemo-resistance is a common cause for poor prognosis and how to improve the chemo- or radio-sensitivity of tumor cells is of great importance to improve survivals of patients under chemo or radiotherapy. In this study, we identified that ADAM12 is elevated in OSCC cells and associated with radio-resistance of OSCC cells. Additionally, miR-29a-3p was found to target and regulate ADAM12 expression in OSCC cells, through which miR-29a-3p regulates the radio-sensitivity of OSCC cells.

The major finding of this study showed that HSC2, HSC4 and SCC4 cell lines had increased expression of ADAM12 when compared with NHOK cells, suggesting ADAM12 may associate with OSCC progression. Consistent with this finding, elevated ADAM12 expression can be found in several tumors, including breast cancer (BC)23 and esophageal cancer24 by increasing the proliferation, metastasis and endocrine resistance of tumor cells. In a study published in 2012, elevated expression of ADAM12 was showed to have certain relationship with TNM classification and enhanced cell malignant behavior of OSCC cells,25 but no current study highlighted the possible role of ADAM12 in radio-resistance of OSCC cells. Further irradiation treatment by 0Gy-20Gy in HSC2 cells demonstrated that ADAM12 expression was increased along with the increased irradiation dosage. The above finding showed that ADAM12 may have a certain role to play in the radio-resistance of OSCC cells. In BC cells, suppression on ADAM12 expression was showed to inhibit p-Akt expression and restore 5-FU sensitivity in 5-FU-resistant BC cells, which contributes to suppressed BC cell survival and invasive abilities.26 In a study exploring the cancer stem cell phenotype in BC cells, knockdown of ADAM12 contributed to suppressed cell migration ability and reduced anoikis resistance.27 Nevertheless, less evidence is available concerned the mechanism of how ADAM12 is regulated in cancer cells.

Online software searched the possible upstream targets of ADAM12 and five miRNAs (hsa-miR-29a-3p, hsa-miR-29b-3p, hsa-miR-217, hsa-miR-29c-3p and hsa-miR-582-5p) were identified. After further detection, miR-29a-3p was eventually selected. The binding of miR-29a-3p with ADAM12 was confirmed by dual luciferase reporter gene assay. Gain- and loss-of-function showed cells transfected with miR-29a-3p overexpression had decreased expression level of ADAM12, while miR-29a-3p inhibition in HSC2 cells led to increased expression level of ADAM12. Those results highlighted the regulatory role of miR-29a-3p in ADAM12 expression in OSCC cells. ADAM12 is well explored in BC cells and a previous study revealed a negative correlation between ADAM12-L and miR-29b/miR-200c.27 In the same study, ADAM12-L 3'UTR was proved to be a direct target gene of miR-29 and miR-200 family members. miR-29a is also a well identified miR involved in virus replication, metastasis and drug resistance.28 In OSCC, down-regulation of miR-29a was associated with lymph node metastasis and TNM stage, in addition to that overexpression of miR-29a was showed to suppress the activity of Wnt/β-catenin pathway.29 Decreased expression of miR-29a was associated with the progression of nasopharyngeal carcinoma, whose up-regulation in nasopharyngeal carcinoma cell line can increase cell sensitivity to Taxol through inhibiting the transcription (STAT) signal pathway and regulating the oncogenic gene Bcl-2.30 The association between miR-29a and drug resistance can also be found in glioblastoma, which highlighted the regulatory role of miR-29a in ameliorating CD133-mediated chemoresistance in glioblastoma stem cells.31 In this study, HSC2 cells transfected with miR-29a-3p overexpression had suppressed cell proliferation and migration ability as well as increased cell apoptosis, while different expression pattern can be found in cells transfected with miR-29a-3p inhibitor. Moreover, co-transfection with miR-29a-3p overexpression and ADAM12 up-regulation can counteract the effect of miR-29a-3p on HSC2 cells, suggesting the regulatory role of miR-29a-3p in mediating cell sensitivity through regulating ADAM12 expression. miR-29a suppression in colorectal cancer was proved to weak drug resistance and increased PTEN expression.32 A similar study showed that overexpression of miR-29a can lead to enhanced sensitivity of HT29/DOX cells to doxorubicin-treatment by targeting membrane transporters P-glycoprotein.33 Although there are studies investigating the mechanism of miR-29a in drug resistance in cancers, mainly in solid tumors, including colon cancer and BC, limited information can be found regarding the possible role and mechanism of miR-29a in mediating cell sensitivity of OSCC.

Taken together, this study highlighted the involvement of miR-29a-3p in mediating cell sensitivity of OSCC. The collected evidence in this study demonstrated that miR-29a-3p enhances the radiosensitivity of OSCC cells through inhibiting AMDM12 expression. Drug resistance involves a complicated mechanism and in study, we only investigated the possible involvement of miR-29a-3p/ADAM12 axis. To better understand the mechanism of OSCC irradiation resistance, a vast number of further studies are needed to enlighten our understating and to facilitate the proposal of better clinical applications to overcome chemoradiation resistance in OSCC.

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