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FBXW7 Enhances Cisplatin-Induced Apoptosis in Oral Cancer Cell Lines

Qi Yang *, *Yang Sun*, *Bo Qiu*, *Huanhuan Zhao*

Dental Clinic, Cangzhou Central Hospital, Cangzhou, Hebei, China

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ABSTRACT

Background: About one-third of patients with oral squamous cell carcinoma (OSCC) have a risk of occurrence and chemoresistance, making survival rates abysmal. We aim to evaluate the role of F-box/WD repeat-containing protein 7 (FBXW7) to further develop efficient treatment of chemoresistant OSCC.

Methods: FBXW7 overexpression was induced in human OSCC cell lines including SCC9 and CAL27 by a lentiviral vector, Lv-FBXW7 or lv-NC (noncoding control), and overexpression efficiency was assessed using quantitative real-time polymerase chain reaction (qRT-PCR) and western blot of FBXW7. Cell viability was measured using MTT assay. The effects of FBXW7 overexpression on cell migration and invasion was evaluated by the colony formation assay and Matrigel assay. Apoptosis of cells with lv-FBXW7 transfection was measured by qRT-PCR and western blot analyses of BAX, BAK, MCL1, and BCL2 expression. Growth rate and cisplatin sensitivity of CAL27 xenografts with or without FBXW7 overexpression was monitored. Ki-67 and PCMA levels—which are biomarkers of intratumoural apoptosis—BAX, MCL1, Beclin1, and LC3I&II—which are autophagy biomarkers—were assessed.

Results: Transfection of lv-FBXW7 in SCC9 and CAL27 cells resulted in increased sensitivity to cisplatin treatment, as evidenced by slower cell proliferation, lower colony formation and invasion, higher apoptosis, and autophagy compared to those transfected with lv-NC. Mice with CAL27 xenografts overexpressing FBXW7 also demonstrated slower tumour growth and upregulation in Ki067 and PCNA. Tumours also showed higher apoptosis and autophagy activities.

Conclusions: FBXW7 overexpression was herein shown to effectively sensitise OSCC cells to cisplatin treatment in vitro and in vivo.

Introduction

Oral squamous cell carcinoma (OSCC) constitutes most cases of oral cancer.[1] It is more common in males than females, but the number of female patients has gradually increased in recent years.[2] Surgery remains the main intervention for OSCC, but chemotherapy and radiotherapy are mostly used for the those with advanced malignancy.[3,4] Due to the inability to detect OSCC early, one-third of patients with OSCC are in an advanced stage and have the risk of chemoresistant recurrent OSCC, resulting in a poor 5-year survival rate of <60%.[5,6] Strategies to delay or block metastasis and sensitise OSCC to chemotherapies, such as the frontline drug cisplatin, are needed to effectively prolong the survival of patients.

F-box/WD repeat-containing protein 7 (FBXW7) is a 40 amino acid protein that plays a critical role in regulating cytosolic misfolded proteins and damaged organelles mediates the ubiquitin-dependent proteolysis of several key regulatory proteins,[7] including those involved in cell division and cell fate determination such as c-Myc, cyclin E1, Notch, and c-Jun.[8-10] FBXW7 was first identified in budding yeast,[11,12] and the human *FBXW7* gene, located at chromosome 4q31q.3, is found to be deleted in 30% of cancers.[13] Such frequent deletion of FBXW7 in cancer, which leads to an increase in genetic instability,[14] a hallmark of human cancers, has intrigued many researchers because of its potential as a tumour suppressor. It is reported that FBXW7 expression negatively correlates with the clinical grade of patients,[15] making it a potential predictive

* *Corresponding author*. Cangzhou Central Hospital, 16 Xinhua West Road, Cangzhou, Hebei, 061000, China.
E-mail address: yangqi19933291992@163.com (Q. Yang).

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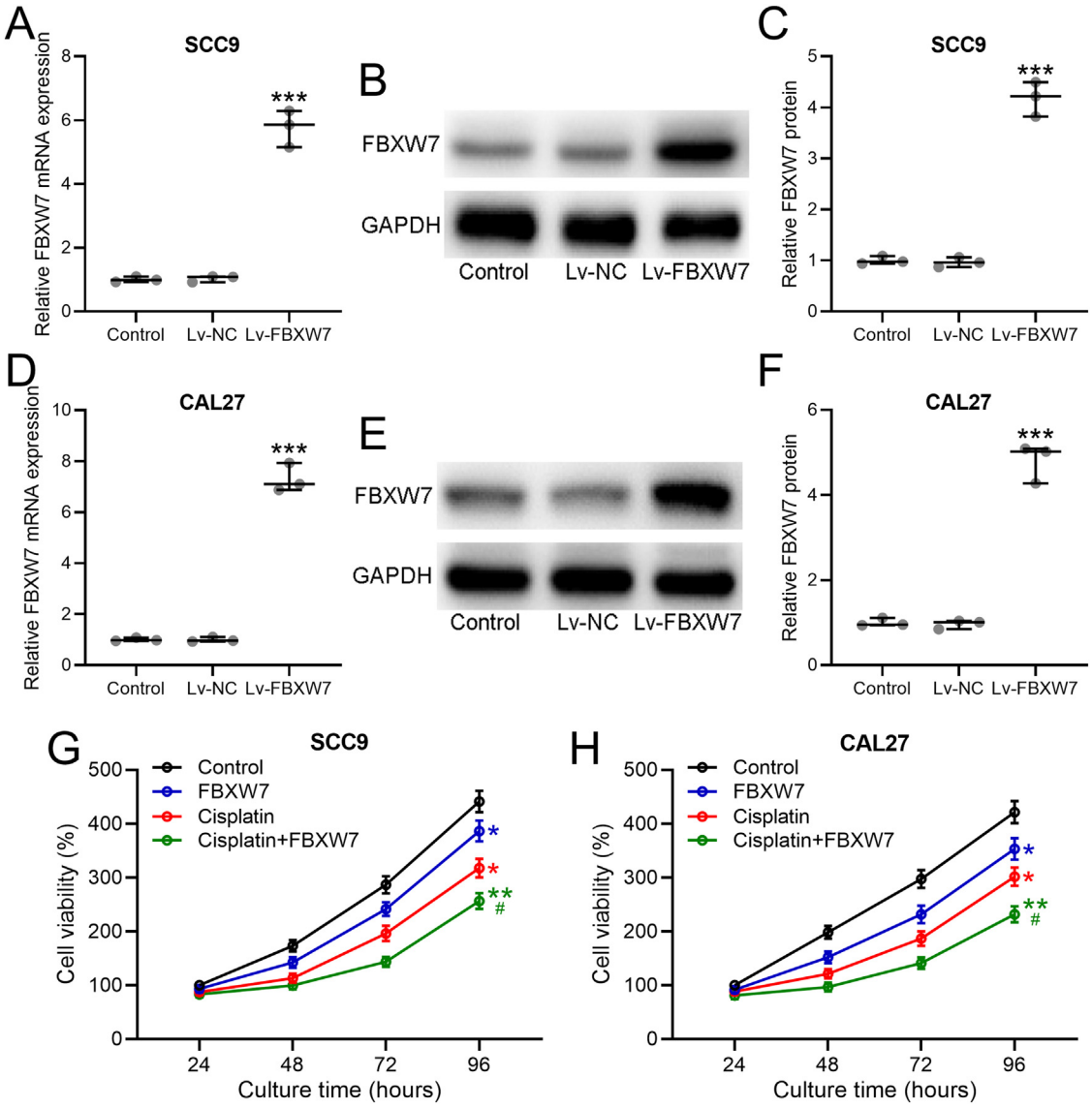

Fig. 1 – F-box/WD repeat-containing protein 7 (FBXW7) enhanced cisplatin-induced inhibition of cell proliferation in SCC9 and CAL27. SCC9 and CAL27 were transfected with LV-FBXW7 or (lv-NC) negative controls for 48 hours. Quantitative real-time polymerase chain reaction was used to measure the levels of FBXW7 mRNA in SCC9 and CAL27 cells (A and D). Western blotting was used to measure the proteins levels of FBXW7 in SCC9 and CAL27 cells (B and E). The expressions were normalised to control (C and F). SCC9 and CAL27 were transfected with LV-FBXW7 and treated with vehicle or 4 μg/mL cisplatin. At 24, 48, 72, and 96 hours after the transfection, cell viability was measured by MTT (G and H). The data are shown as median (interquartile range). $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$ compared to control. $^{\#}P < .05$ compared to cisplatin group.

marker. By comparing the expression of autophagy biomarkers, including MCL1, BECN1, and ATG7,[16] between OSCC tissues and adjacent normal tissues, it is found that the expression of MCL1 was significantly higher, whilst the expression of BECN1 and ATG7 mRNA was significantly lower, suggesting a decreased autophagy activity. MCL1 mRNA expression also showed a significant negative correlation with FBXW7 mRNA levels, whilst BECN1 and ATG7 mRNA expression were significantly positively correlated with FBXW7 levels. In another work, overexpressing FBXW7 in the OSCC cell lines and tumours was shown to inhibit cancer cell proliferation and promote autophagy.[7] Besides, the ability of FBXW7 overexpression in enhancing temozolomide sensitivity in glioma has been demonstrated.[17]

Based upon these findings on the anti-tumour role of FBXW7, we herein aimed to investigate the effects of FBXW7 in enhancing the antitumour efficacy of cisplatin on OSCC cells. We focussed on evaluating whether FBXW7 overexpression using a lentiviral vector could inhibit cancer proliferation, migration, and invasion and enhance OSCC's sensitivity to cisplatin by increasing apoptosis and autophagy. The

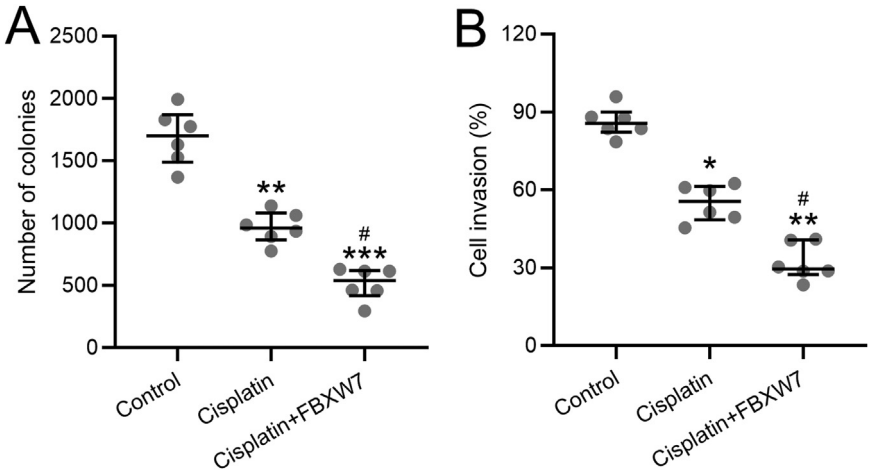

Fig. 2 – F-box/WD repeat-containing protein 7 (FBXW7) enhanced cisplatin-induced inhibition of cell proliferation and invasion of CAL27. CAL27 were transfected with LV-FBXW7 and treated with 4 μg/mL cisplatin. A, The colony formation assay was conducted 10 days after transfection followed by counting colonies. (B) Cell invasion capabilities were measured 48 hours after treatment and the cell invasion ratio were calculated. The data are shown as median (interquartile range). $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$ compared to control. $^{\#}P < .05$ compared to cisplatin group.

results of the study could potentiate the use of FBXW7 overexpression to improve the survival of patients with OSCC.

Materials and methods

Cell culture and cisplatin treatment

Human OSCC cell line CAL27, SCC9 was acquired from American Type Culture Collection (ATCC) and was cultured in RPMI-1640 medium with 10% fetal bovine serum (Gibco) and 1% penicillin/streptomycin. Cells were cultured in a 37 °C humidified incubator with 5% CO_2. For cisplatin treatment, CAL27 cells transfected with Lv-FBXW7 plasmids or control plasmids were treated with vehicle phosphate-buffered saline or 4 μg/mL cisplatin based on previous protocols.[18]

Ectopic overexpression of FBXW7

Construction of Lv-FBXW7 overexpression vector was conducted in reference to a previous protocol.[19] Briefly, human FBXW7 complementary DNA was reversely transcribed from the longest transcript NM_013233 containing all 3 isoform-encoding sequences (GAGGATCCCCGGGTACCGGTCGCCACCATGAATC). The cDNA was inserted into the lentiviral vector GV358 (purchased from Genechem) to create the complete functional overexpression plasmid named Lv-FBXW7. Another noncoding control lentiviral vector was also constructed as Lv-NC. Conditioned medium containing lentiviruses was harvested 48 hours from transfected 293T cells and prepared for further transfection.

Animal studies

CAL27 tumour xenografts were grown in mice according to a previous protocol.[20] Briefly, BALB/c nude mice aged 4 to 6 weeks were subcutaneously injected with 5×10^6 CAL27 cells that were transfected with Lv-FBXW7 expression plasmids in 100 μL phosphate-buffered saline. The cells were divided into 3 groups: the control group, the cisplatin-treated group, and the group transfected with FBXW7 and treated with cisplatin. Cisplatin treatment was started from the day after cell injection, and the mice were intraperitoneally injected with vehicle or 5 mg/kg body weight cisplatin. The treatment was performed every 3 days from day 1 to day 28. Animal studies were approved by the institutional animal care and use committee of Cangzhou Central Hospital.

Quantitative real-time polymerase chain reaction (RT-PCR)

DNA was extracted using the TIZOL agent and reversely transcribed. The SYBR Green mix was used in RT-PCR. The following primers were used: FBXW7, forward, 5′-ACTGGGCTTGTACCATGTTCA-3′ and reverse, 5′-TGAGGTCCCCAAAAGTTGTTG-3′; GAPDH, forward, 5′-TGTTGCCATCAATGACCCCTT-3′ and reverse, 5′-CTCCACGACGTACTCAGCG-3′; MCL1, forward, TGCTTCGGAAACTGGACATCA; reverse, TAGCCACAAAGGCACCAAAAG; PCNA, forward, GGCTCTAGCCTGACAAATGC; reverse, GCCTCCAACACCTTCTTGAG; Ki67, forward, AAGCCCTCCAGCTCCTAGTC; reverse, TCCGAAGCACCACTTCTTCT; BAK, forward, GTTTTCCGCAGCTACGTTTTT; reverse, GCAGAGGTAAGGTGACCATCTC; BAX, forward, CCCGAGAGGTCTTTTTCCGAG; reverse, CCAGCCCATGATGGTTCTGAT; BCL2, forward, GGTGGGGTCATGTGTGTGG; reverse: CGGTTCAGGTACTCAGTCATCC.

Statistics

The data are shown as median (interquartile range). Data were analysed with 1- or 2-way analysis of variance with a post hoc test. Statistical significance was determined when the *P* value was <.05.

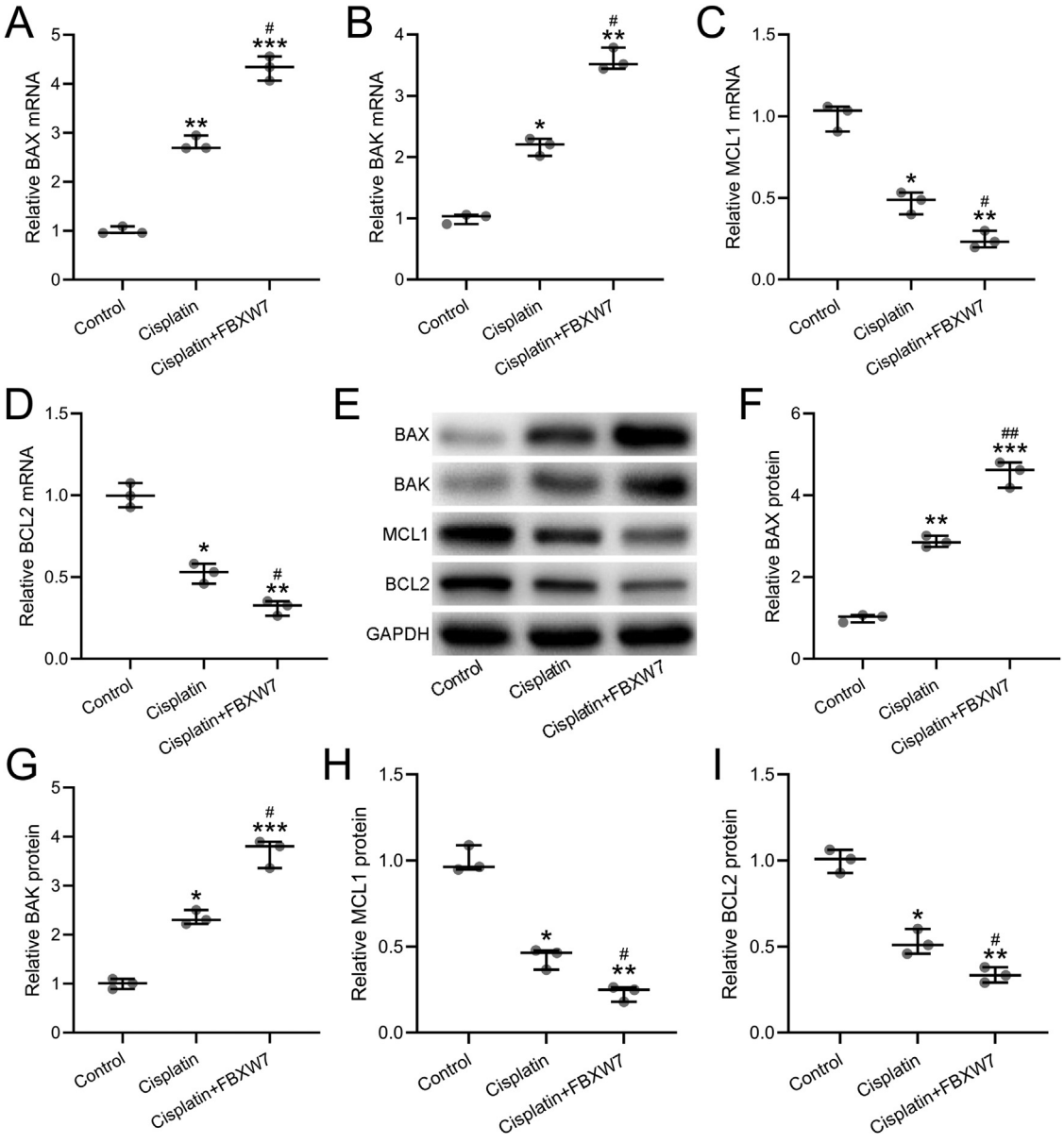

Fig. 3 – F-box/WD repeat-containing protein 7 (FBXW7) enhanced cisplatin-induced apoptosis of CAL27. CAL27 were transfected with LV-FBXW7 and treated with 4 μg/mL cisplatin for 48 hours. The mRNA levels of BAX, BAK, MCL1, and BCL2 were measured by real-time polymerase chain reaction (A–D). The protein level of proapoptotic molecules BAX, BAK, and anti-apoptotic molecules MCL1 and BCL2 were examined by western blot (E). The expressions were normalised to control (F–I). The data are shown as median (interquartile range). *P < .05; **P < .01; ***P < .001 compared to control. #P < .05; ##P < .01 compared to cisplatin group.

Results

FBXW7 enhances cisplatin-induced inhibition of cell proliferation in OSCC

We first validated the overexpression of FBXW7 in OSCC cells including SCC9 (Figure 1A–1C) and CAL27 (Figure 1D–1F). After transfecting Lv-FBXW7 in SCC9 cells, the expression of FBXW7 was upregulated ~6 fold in the mRNA level and ~4 fold in the protein level ($P < .001$) (Figure 1A and Figure 1C). Upregulation was also prominent in CAL27 cells, with a ~6.5 fold upregulation in the mRNA level and ~5 fold in the protein level ($P < .001$) (Figure 1D and 1F). The enhancing effects of FBXW7 overexpression on cisplatin treatment were investigated by MTT assay, which found that despite that cisplatin-treated cells show continual but slower growth than untreated cells, and FBXW7 was effective in retarding proliferation of treated and untreated OSCC cell lines (Figure 1G and 1H). This suggests that FBXW7 can inhibit cell proliferation either by itself and in concert with cisplatin.

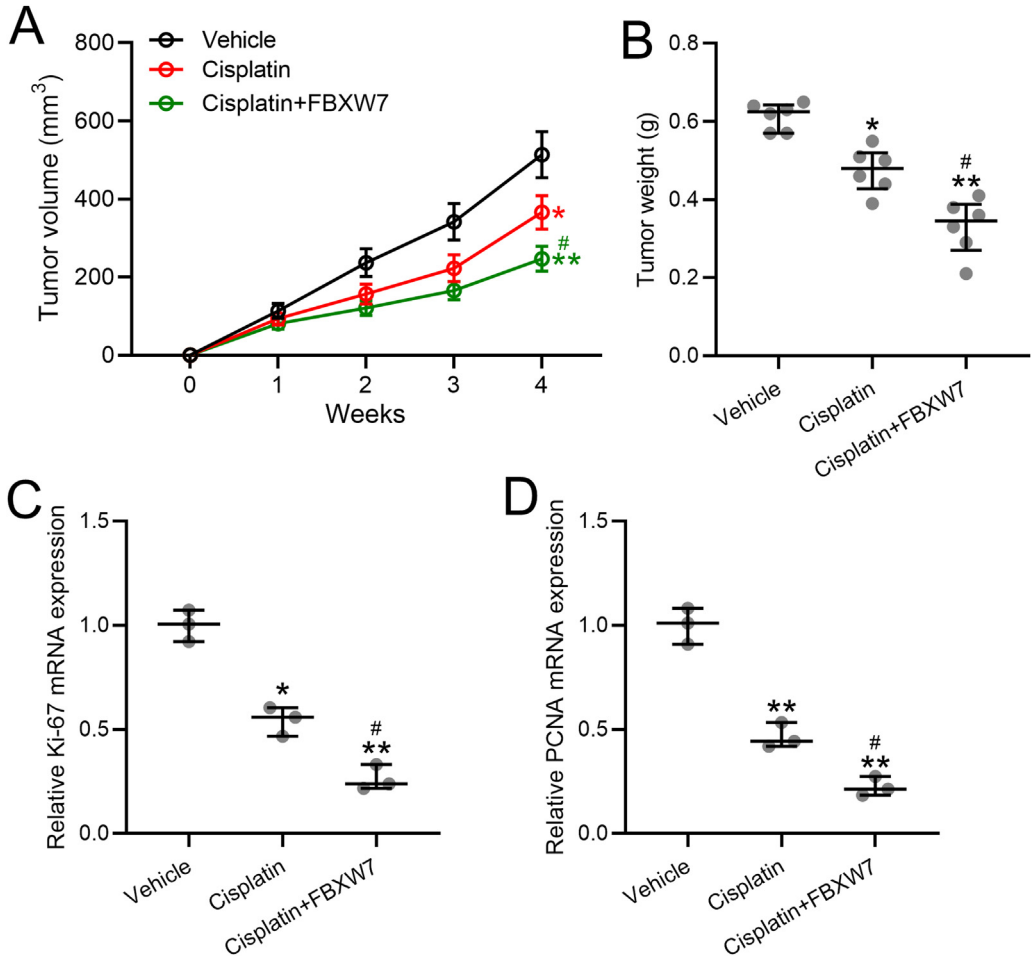

Fig. 4 – F-box/WD repeat-containing protein 7 (FBXW7) enhanced cisplatin-induced inhibition of cell proliferation of CAL27 in vivo. CAL27 xenograft tumour model was set up in Balb/c nude mice. CAL27 cells (5 × 10^6/mouse) transfected with and without Lv-FBXW7 were injected subcutaneously into the flanks of the nude mice (n = 6 in each group). Cisplatin or vehicle was intraperitoneally injected at 5 mg/kg body weight every 3 days from day 1 to 28. The tumour growth curve (A) and tumour weight at day 28 (B) are shown. Quantitative real-time polymerase chain reaction was used to measure the mRNA levels of Ki67 (C) and PCNA (D) in the tumour homogenate from each group. The data are shown as median (interquartile range). *P < .05; **P < .01 compared to vehicle. #P < .05 compared to cisplatin group.

OSCC colony formation and invasion are further reduced in cisplatin-treated cells after FBXW7 expression

Cell migration and invasion were assessed by the clonogenic assay and Matrigel cell invasion assay. Cells treated with cisplatin together with FBXW7 overexpression showed lower colony-forming abilities (Figure 2A) and invasion (Figure 2B), compared to untreated and cisplatin-treated cells, as evidenced by significantly reduced number of colonies and invaded cells. These data indicated that FBXW7 overexpression enhanced the effects of cisplatin in inhibiting cell migration and invasion.

FBXW7 overexpression enhanced cisplatin-induced apoptosis in OSCC

The apoptosis of CAL27 cells was further evaluated in cells with overexpression of FBXW7 and cisplatin treatment by analyzing mRNA (Figure 3A-3D) and protein (Figure 3E-3I) levels of apoptosis biomarkers including BAX (Figure 3A), BAK (Figure 3B), MCL1 (Figure 3C), and BCL2 (Figure 3D). As shown in Figure 3, it is evident that FBXW7 overexpression enhanced the cisplatin-induced apoptosis of CAL27 cells, evidenced by upregulation of BAX and BAK and downregulation of MCL1 and BCL2.

FBXW7 overexpression sensitises OSCC tumours to cisplatin treatment

The ability of FBXW7 to enhance antitumour effect of cisplatin on OSCC was next evaluated in vivo. Tumour volume was monitored for 4 weeks, after which tumour weight was measured after sacrificing the mice. Whilst cisplatin reduced tumour growth rate ($P < .05$; Figure 4A) and tumour weight ($P < .05$; Figure 4B) compared to vehicle-treated mice, greater reductions were seen in mice with FBXW7-overexpressing tumours ($P < .01$ compared to vehicle-treated mice) as shown by pronounced slower tumour growth (Figure 4A) and smaller

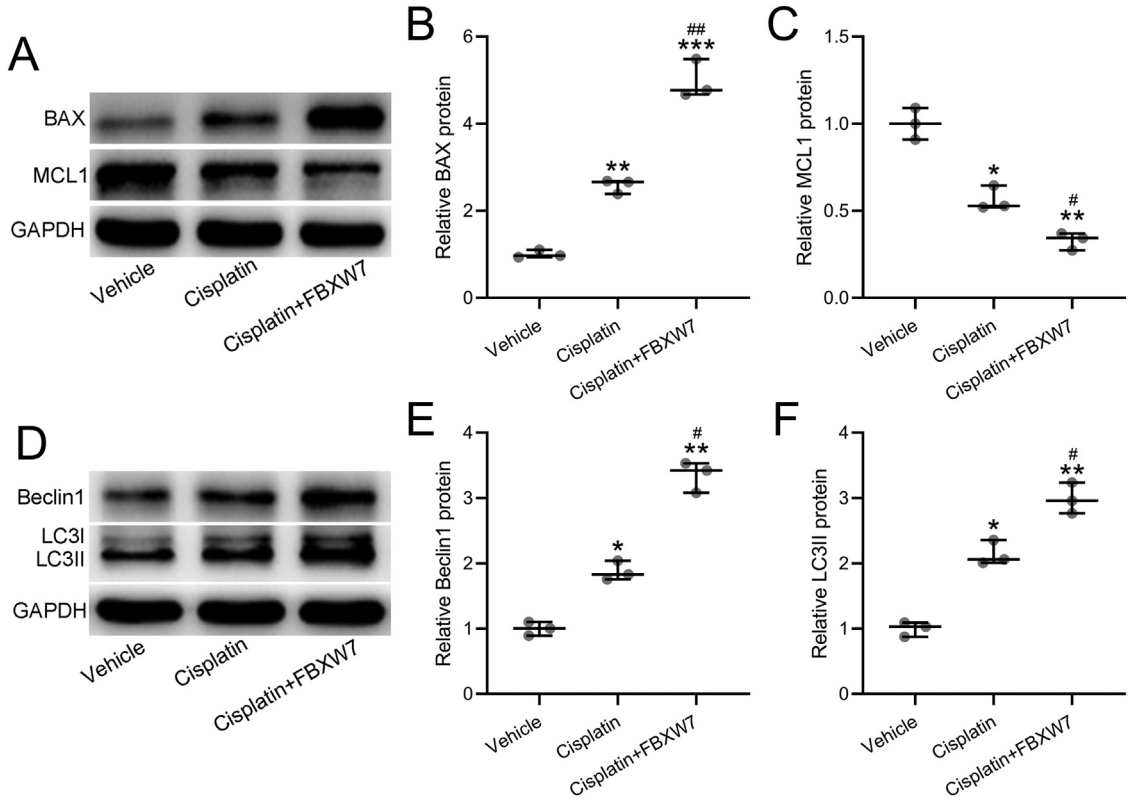

Fig. 5 – F-box/WD repeat-containing protein 7 (FBXW7) enhanced cisplatin-induced apoptosis and autophagy of tumour tissues in vivo. CAL27 xenograft tumour model was set up in Balb/c nude mice. CAL27 cells (5×10^6/mouse) transfected with and without Lv-FBXW7 were injected subcutaneously into the flanks of the nude mice (n = 6). Cisplatin or vehicle was intraperitoneally injected at 5 mg/kg body weight every 3 days from day 1 to 28. The protein level of proapoptotic molecules BAX and anti-apoptotic molecules MCL1, autophagy-related protein levels of Beclin1 and LC3 were examined by western blot (A and D). The expressions were normalised to control (B, C, E, F). The data are shown as median (interquartile range). $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$ compared to vehicle. $^{\#}P < .05$; $^{\#\#}P < .01$ compared to cisplatin group.

tumour at 4 weeks (Figure 4B). Our data suggested that FBXW7 overexpression indeed led to slower tumour progression in cisplatin-treated mice ($P < .05$ compared to those without FBXW7 overexpression). The reduced Ki67 (Figure 4C) and PCNA (Figure 4D) levels measured by RT-PCR also confirmed the enhancing effects of FBXW7 overexpression in OSCC ($P < .05$ compared to those without FBXW7 overexpression).

FBXW7 enhanced cisplatin-induced apoptosis and autophagy of tumour tissues in vivo

We next evaluated the apoptosis and autophagy levels in the harvested tumour by measuring expression of BAX, MCL1 (apoptosis markers, Figure 5A–5C), Beclin1, and LC3I&II (Figure 5D–5F). Our data suggested that FBXW7 amplified the cisplatin-induced apoptosis and autophagy in OSCC tumour tissues, as evidenced by significantly increased expression of BAX ($P < .001$ compared to vehicle-treated cells and $P < .01$ compared to cisplatin-treated cells) and Beclin1 ($P < .01$ compared to vehicle-treated cells and $P < .05$ compared to cisplatin-treated cells), as well as decreased expression of MCL1 and LC3II ($P < .01$ compared to vehicle-treated cells and $P < .05$ compared to cisplatin-treated cells).

Discussion

To overcome chemoresistance of OSCC, one of the important factors contributing to treatment failure,[21] we explored FBXW7 overexpression as a new strategy for sensitising OSCC to cisplatin treatment.[22] Our in vitro study showed that FBXW7 overexpression was capable of suppressing cell proliferation, migration, and invasion in cells with cisplatin treatment. Such tumour-suppressing and cisplatin-sensitising function was further supported by in vivo study, which showed retarded tumour growth and enhanced tumour apoptosis and autophagy. These data suggest the significant clinical implication of FBXW7 in OSCC.

Apoptosis, autophagy, and necrosis are 3 classic cell-death pathways, which are the mechanisms of cisplatin's anticancer efficacy. Our results showed that FBXW7 promoted cell death by enhancing cisplatin-induced cell death. In cancer, autophagy plays opposing roles, as autophagy—through degrading organelles and cytoplasmic constituents—on the one hand inhibits tumourigenesis and on the other hand induces metastasis and chemotherapy resistance. Anticancer drugs, including cisplatin, are found to induce autophagy, a mechanism cancer cells exploit to acquire chemoresistance. Hence, autophagy has been pursued as a therapeutic target to

develop novel anticancer drugs.[23,24] Several studies have investigated FBXW7 as a regulator of autophagy in human diseases, including cancer.[25-27] In lung cancer, targeting FBXW7 by miR-223 was shown to inhibit cisplatin-induced autophagy.[18] In studying hepatocarcinoma, FBXW7 overexpression effectively inhibited sorafenib resistance through inhibiting autophagy.[28] Our findings corroborated FBXW7 as not only a tumour suppressor but also an autophagy enhancer in OSCC, which contradicts the aforementioned studies; this could be explained by the complex role of autophagy.

Several limitations should be noted. Despite that FBXW7 overexpression by directly transfecting lentiviral vector is proven successful for in vitro study, such an approach is not translatable, as the delivery of FBXW7 overexpressing vector to tumour cells is crucial for efficient gene transduction. However, with advances in gene delivery technologies, it is feasible to develop a gene vector—either viral or nonviral—for targeted delivery of FBXW7 plasmid to cancer. Further, the exact molecular mechanism of how FBXW7 regulates autophagy remains to be elucidated. Exploring the effects of FBXW7 in reducing cisplatin resistance in animal models of advanced OSCC is also warranted.

In conclusion, by overexpressing FBXW7 in OSCC, we have shown that FBXW7 is a tumour suppressor and can sensitise OSCC to cisplatin treatment. FBXW7 overexpression enhanced the effects of cisplatin in inhibiting OSCC cell proliferation, migration, and invasion in vitro and also resulted in slower tumour growth and higher apoptosis and autophagy in vivo. Our data support further investigate into the role of FBXW7 overexpression in OSCC clinical settings.

Conflict of interest

None disclosed.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.identj.2022.11.008.

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