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Original Article

Long non-coding RNA PP7080 enhances cancer stemness and tumorigenic features in oral cancer

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Abstract *Background/purpose:* Emerging evidence has shown that various failures in cancer therapy, such as drug resistance, metastasis, and cancer relapse are attributed to cancer stem cells (CSCs). Also, growing attention has been paid to the regulation of non-coding RNAs in cancer stemness. Here, we aimed to investigate the impact of lncRNA PP7080 on cancer stemness in oral squamous cell carcinomas.
Materials and methods: PP7080 expression was assessed in ALDH1$^+$ and ALDH1$^-$ cells sorted from oral squamous cell carcinoma cell lines using qRT-PCR. PP7080 was silenced in ALDH1$^+$ SAS cells, and the effects on stemness characteristics, including ALDH1 activity, cell migration, colony formation, CD44 and Oct4 expression, and the expression of drug resistance-related markers ABCG2 and Bmi-1, were examined. The interaction between PP7080 and miR-601 was validated using a luciferase reporter assay. Rescue experiments were performed by inhibiting miR-601 in PP7080-silenced cells using apoptosis analysis. PP7080 expression in HNSCC was analyzed using the TCGA-HNSCC database.
Results: Our results showed that PP7080 was significantly overexpressed in oral cancer tissues

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and positively correlated with stemness markers. The phenotypic and flow cytometry assays demonstrated that suppression of PP7080 reduced the migratory and colony-forming aibilities, cancer stemness features, and self-renewal abilities in oral CSCs. Furthermore, we demonstrated that PP7080 may enhance cancer stemness features by counteracting the tumor-suppressive effect of miR-601.

Conclusion: Targeting PP7080 may offer a promising therapeutic strategy for oral cancer by reducing cancer stemness.

Introduction

Oral cancer remains a significant global health concern, characterized by high rates of metastasis and poor patient prognosis. One of the key factors responsible for tumor recurrence, resistance to therapy, and metastatic dissemination is the existence of a distinct subpopulation of tumor-initiating cells, referred to as cancer stem cells (CSCs).[1] These CSCs exhibit self-renewal capacity and the ability to differentiate into diverse tumor cell types, mirroring the regulatory networks of embryonic stem cells through the expression of key pluripotency-associated transcription factors like Oct4, Sox2, and Nanog. Consequently, CSCs are recognized as pivotal drivers of oral cancer progression and a major impediment to effective treatment.[2]

In oral squamous cell carcinoma (OSCC), CSCs can be identified and enriched based on the expression of specific cell surface markers such as CD44 and aldehyde dehydrogenase 1 (ALDH1).[3] Clinically, elevated expression of CD44 and ALDH1 in OSCC patients are strongly correlated with adverse clinical outcomes, including increased lymph node metastasis, reduced overall survival, advanced disease stage, and poor therapeutic response.[4,5] Notably, OSCC cells co-expressing CD44 and ALDH1 are often linked to mesenchymal-like features and increased motility, suggesting a close relationship with the epithelial—mesenchymal transition (EMT) —a biological process in which epithelial cells acquire invasive and migratory properties.[6] While EMT plays a critical role in metastasis, it also contributes to the acquisition and maintenance of CSC phenotypes.[7] Similarly, autophagy, another key cellular process, has been shown to intersect with CSC regulation.[8] For instance, Bmi-1, a polycomb group protein, promotes CSC self-renewal and drug resistance and has also been linked to autophagic modulation in head and neck cancers.[9] Thus, CSCs lie at the intersection of multiple biological networks critical to oral cancer progression.[10,11] Previous study has shown that, in head and neck squamous cell carcinoma (HNSCC), Bmi-1 is overexpressed in $ALDH1^+$ CSCs and has been implicated in conferring resistance to chemoradiotherapy and promoting tumorigenicity.[12] Conversely, silencing of Bmi-1 enhances apoptosis, restores treatment sensitivity, and suppresses tumor growth *in vivo*,[13] highlighting its central role at the intersection of CSC maintenance and autophagy regulation.

Mounting evidence highlights the significant role of non-coding RNAs in the intricate regulatory networks governing cancer development, including cancer stemness.[14,15] Long non-coding RNAs (lncRNAs), transcripts exceeding 200 nucleotides, are known to govern critical cellular processes such as cell cycle regulation, differentiation, proliferation, and apoptosis. LncRNAs have been implicated in the regulation of cancer stemness through interaction with microRNAs (miRNAs, 18—22 nucleotides in length), which target gene stability by binding to complementary sites in the 3′ untranslated region (3′-UTR), leading to transcript degradation.[16] Through specific microRNA response elements (MREs), lncRNAs can titrate and sequester miRNAs, thereby alleviating the miRNAs' suppressive effects on their target mRNAs.[17] LncRNA PP7080 was initially reported to be downregulated in colon adenocarcinoma, suggesting its potential as a diagnostic and prognostic biomarker.[18] However, subsequent studies have revealed upregulated PP7080 expression in other cancers, such as hepatocellular carcinoma (HCC) and lung adenocarcinoma, with its upregulation in HCC correlating with poor prognosis.[19,20] Mechanistically, PP7080 has been shown to directly target miR-601 in HCC cells, thereby promoting cell proliferation, migration, and invasion while reducing apoptosis,[19] indicating a significant role for PP7080 in cancer progression. Given the pivotal role of CSCs in various aspects of OSCC development, the expression and biological function of lncRNA PP7080 in oral cancer remain largely underexplored. Therefore, the present study aimed to investigate the role of lncRNA PP7080 in mediating cancer stemness features in oral carcinomas. We hypothesize that PP7080 contributes to the maintenance of CSC characteristics through interaction with miR-601, and its suppression may reduce stem-like traits and therapeutic resistance in oral cancer cells.

Materials and methods

Cell culture and cancer stem cell establishment

Human tongue and gingival squamous cell carcinoma cell lines, SAS cells and Ca9-22 cells were cultured with Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F12) and DMEM respectively supplemented with 1 % PSA and 10 % FBS (Gibco, Thermo Fisher Scientific, Waltham, MA, USA). SAS-CSC was establish as previous

described. Briefly, SAS-CSCs were enriched in a spheres forming condition with serum-free culture medium supplemented 0.1 % bFGF, 0.1 % EGF (Invitrogen Life Technologies, Carlsbad, CA, USA), and 1 % N_2 (R&D Systems Inc., Minneapolis, MN, USA). CSCs were validated through the expression of stemness markers, including CD44, and ALDH1 enzymatic activity.[21]

Flow cytometry analysis

Flow cytometry was employed to isolate ALDH1-positive ($ALDH1^+$) cells and assess ALDH1 enzymatic activity using the ALDEFLUOR™ assay kit (StemCell Technologies Inc., Vancouver, BC, Canada), following the manufacturer's instructions. Cell sorting was performed using a FACSAria™ II cell sorter (BD Biosciences, San Jose, CA, USA). To evaluate the expression levels of ABCG2 and CD44, cells were stained with phycoerythrin (PE)-conjugated anti-CD44 antibody (BD Biosciences) and fluorescein isothiocyanate (FITC)-conjugated anti-ABCG2 antibody (Millipore, Merck, Darmstadt, Germany). Apoptotic cells were identified using the Annexin V-FITC Apoptosis Detection Kit (BD Biosciences), which includes dual staining with Annexin V-FITC and propidium iodide (PI). Fluorescence signals were detected using a FACSCalibur™ flow cytometer (Becton Dickinson), and data were analyzed with CellQuest™ software.[22]

Quantitative real-time PCR (qRT—PCR) analysis for expression detection

Total RNA was extracted from cells using TRIzol reagent following the manufacturer's instructions (Invitrogen Life Technologies). Complementary DNA (cDNA) was synthesized from mRNA using the SuperScript™ III First-Strand Synthesis System (Invitrogen Life Technologies). Quantitative real-time PCR (qRT-PCR) was subsequently conducted on the synthesized cDNA using the ABI StepOne™ Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA). The primers for PP7080 were AGGTGTTGGTGGGAGTGTTG (forward) and CAGAAGCTGAGTCCAGGCAA (reverse), and for GAPDH were CTGGTGGCTGGCTCAGAAAA (forward) and GGGAGATTCAGTGTGGTGGG (reverse).[19]

MiR-601 transfection and inhibition

To modulate miR-601 expression, synthetic miR-601 mimic, miR-601 inhibitor, and a non-targeting scrambled miRNA control were obtained from Thermo Fisher Scientific (Carlsbad, CA, USA). Cell transfection was performed using Lipofectamine™ 2000 reagent (Invitrogen Life Technologies) in accordance with the manufacturer's protocol. The scrambled miRNA was used as a negative control.

Lentiviral-mediated RNA interference (RNAi) for silencing PP7080

The pLV-RNAi vector was obtained from Biosettia Inc. (San Diego, CA, USA). Cloning of the double-stranded short hairpin RNA (shRNA) sequence was performed in accordance with the manufacturer's instructions. A synthesized oligonucleotide sequence encoding shRNA targeting human PP7080 was inserted into the pLV-RNAi vector to construct the lentiviral shRNA expression plasmid.[23]

Migration and soft agar colony formation assay

These assays are well-established in our laboratory, and all procedures were performed in accordance with previously described protocols.[24,25]

Statistical analysis

Statistical analyses were performed using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as the mean ± standard deviation (SD). To determine statistical significance between experimental groups, either Student's t-test or one-way ANOVA followed by Dunnett's post-hoc test were employed. A *P*-value of less than 0.05 was considered statistically significant.

Results

To investigate the involvement of lncRNA PP7080 in oral cancer stemness regulation, we first assessed its expression in $ALDH1^+$ and $ALDH1^-$ cell population sorted from SAS and Ca9-22 cell lines. As shown in Fig. 1A, PP7080 expression was significantly elevated in $ALDH1^+$ cells compared to $ALDH1^-$ cells in both lines, highlighting its potential association with CSC-like properties (Fig. 1A). Based on this, we examined the CSC markers of PP7080 by silencing its expression in $ALDH1^+$ SAS cells using two independent shRNAs. qRT-PCR confirmed the effective knockdown, revealing a significant reduction in PP7080 expression in both groups compared to the control vector (Fig. 1B). Silencing PP7080 significantly reduced ALDH1 activity as shown by flow cytometry analysis with or without the ALDH1 inhibitor DEAB (Fig. 1C). Similarly, $CD44^+$ cell population was markedly decreased in both knockdown groups compared to Sh-Luc (Fig. 1D). These findings demonstrate that lncRNA PP7080 is involved in the regulation of key CSC markers in $ALDH1^+$ SAS cells.

Given the established role of CSCs in promoting tumor progression, we further investigated the functional effects of PP7080 using shRNA-transfected $ALDH1^+$ SAS cells. Fig. 2A revealed a significant reduction in the transwell migration assay in PP7080-silenced groups compared to the control group. Furthermore, the soft agar colony formation assay showed a substantial decrease in the relative colony-forming unit (C.F.U.) upon PP7080 silencing (Fig. 2B), suggesting that PP7080 contributes to the tumorigenic and metastatic potential linked to stem-like properties. The expression of ABCG2, a known drug resistances-related transporter and potential CSC marker was examined. Flow cytometric indicated a significant decrease in ABCG2-positive cell upon PP7080 silencing (Fig. 2C), suggesting PP7080 may influence drug resistance-related characteristics in $ALDH1^+$ SAS cells. The protein expression levels of key stemness-associated transcription factors were then validated using Western blot analysis. Fig. 2D revealed a notable downregulation of Oct4 and Bmi-1 protein levels in PP7080-silenced groups. Given the established involvement of Bmi-1 and Oct4 in metastasis and poor survival in OSCC, these findings suggest

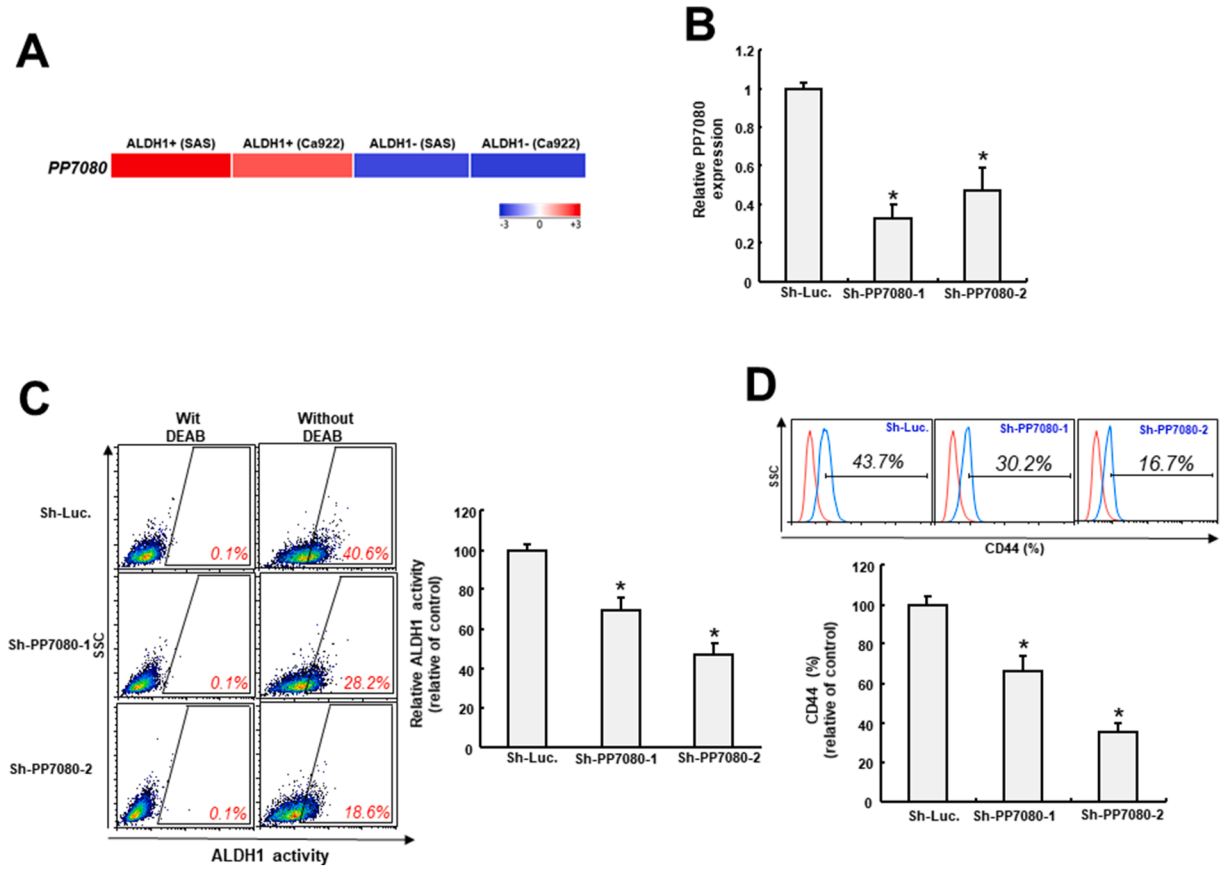

Figure 1 PP7080 is upregulated in ALDH1$^+$ OSCCs and positively correlated with stemness markers. (A) PP7080 expression was positively associated with ALDH1$^+$ cell populations in SAS and Ca9-22 cell lines. (B) Knockdown efficiency of PP7080 in SAS cells (Sh-PP7080-1/2) compared to a control (Sh-Luc.) (C) ALDH1 activity in SAS cells with or without DEAB, the ALDH1inhibitor. Bar graph represents the relative ALDH1 activity normalized to the control group. (D) CD44 expression level in SAS cells. *$P < 0.05$ compared with Sh-Luc.

that PP7080 may modulate stem-like phenotypes by regulating Oct4 and Bmi-1 in ALDH1$^+$ OSCC cells.

Based on previous findings in hepatocellular carcinoma indicating that lncRNA PP7080 can directly target miR-601,[19] we investigated this interaction in OSCC to elucidate PP7080's role in stemness. We first identified the predicted miR-601 binding site on PP7080 (Fig. 3A). Luciferase assays in ALDH1$^+$ SAS cells with wild-type or mutated reporters showed that miR-601 overexpression significantly reduced luciferase activity of the wild-type reporter, but this reduction was abolished with the mutated reporter (Fig. 3B). These findings confirm a direct interaction between PP7080 and miR-601 in ALDH1$^+$ SAS cells.

To verify the role of PP7080 in self-renewal ability through miR-601, we performed sphere-forming assays. ALDH1$^+$ SAS cells with stable PP7080 knockdown (Sh-PP7080) were transfected with either a miR-601 mimic as an inhibitor or a scrambled control (miR-Scr.). As shown in Fig. 4A, PP7080 knockdown significantly reduced sphere formation compared to the control (Sh-Luc.). However, inhibition of miR-601 in PP7080-knockdown cells partially rescued the sphere-forming ability, suggesting that PP7080 promotes self-renewal at least in part by suppressing miR-601.

To further investigate the impact of PP7080 and miR-601 on cell survival, we conducted apoptosis assays using Annexin V and propidium iodide (PI) staining. PP7080 knockdown significantly increased the percentage of apoptotic cells compared to the control. Notably, this increase in apoptosis was partially reversed by inhibiting miR-601 in the PP7080-knockdown cells (Fig. 4B). These findings indicate that PP7080 may promote cell survival, at least partially, by negatively regulating miR-601.

To assess the clinical relevance of PP7080 in HNSCC, we analyzed its expression using The Cancer Genome Atlas (TCGA-HNSC) database. Our analysis revealed a significant upregulation of PP7080 expression in tumor tissues compared to normal tissues (Fig. 5A). Furthermore, PP7080 expression was significantly elevated across different tumor stages (Stage I-IV) compared to normal tissues (Fig. 5B). Similarly, PP7080 expression was significantly elevated in tumor grades G1-G3 compared to normal tissues (Fig. 5C). These findings suggest that PP7080 upregulation is associated with HNSCC and may play a role in tumor progression.

Discussion

The significant roles of non-coding RNAs are increasingly being recognized as critical layers of post-transcriptional regulation in cancer stem cell biology.[14,15] This study

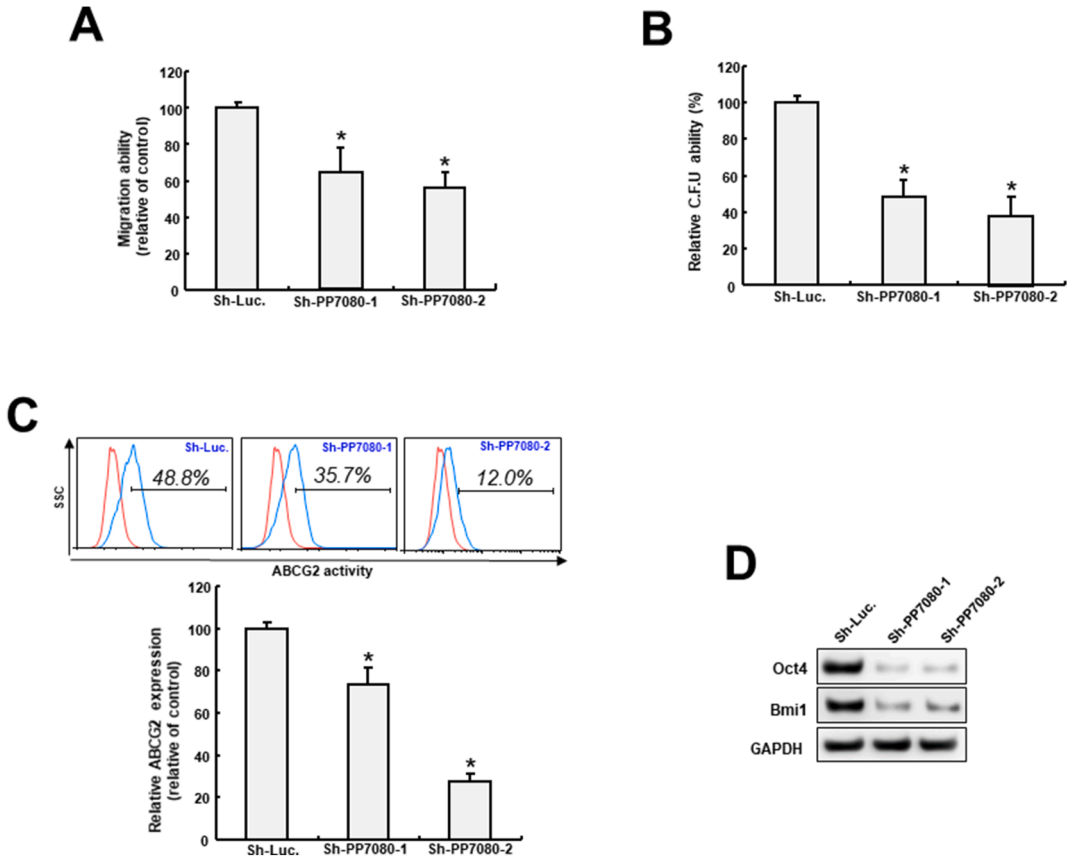

Figure 2 PP7080 knockdown inhibits migration, colony formation, and reduces ABCG2, Oct4, and Bmi1 expression in SAS cells. (A) Transwell migration assay and (B) soft agar colony formation assay and the quantification. (C.F.U, colony-formating unit) (C) Flow cytometric analysis of ABCG2 expression. *$P < 0.05$ compares with Sh-Luc. (D) Western blot analysis of Oct4 and Bmi1 protein levels in SAS cells.

provides novel evidence for the lncRNA PP7080's specific role in regulating cancer stemness within OSCC, building upon the established prognostic significance of stem cell biomarkers such as ALDH1 activity, CD44, Oct4, Nanog, and Bmi-1 in various cancers.[4,5,26] While the precise molecular mechanisms governing CSC regulation remain largely unclear, necessitating the identification of potential therapeutic targets, our findings indicate that PP7080 influences key CSC characteristics, including cell motility, colony formation, self-renewal, and the expression of stemness and drug resistance markers in ALDH1$^+$ OSCC cells. Consistent with previous reports demonstrating PP7080's role in promoting aggressiveness in HCC,[19] gastric[27] and lung cancers,[20] we observed elevated PP7080 expression in OSCC tumor tissues and a positive correlation with HNSCC in the TCGA database. Mechanistically, our data suggest that PP7080 exerts these effects, at least in part, by sequestering miR-601, a mechanism also implicated in HCC development through the targeting of SIRT1,[19] a histone deacetylase. However, SIRT1 has been reported tumor suppressor and is associated with Cisplatin resistance in OSCC.[28] In our model, miR-601 inhibition only partially rescued PP7080 knockdown-induced apoptosis, suggesting PP7080/miR-601 regulatory axis in OSCC may involve additional downstream pathways. Further investigation is needed to clarify this mechanism.

The critical roles of EMT and CSCs in cancer metastasis, a major contributor to the high mortality rate in OSCC patients, are well-recognized.[9] In addition to the observed decrease in Oct4 upon PP7080 silencing, previous research has demonstrated that Bmi-1 knockdown in ALDH$^+$ CSCs leads to the downregulation of other critical stemness markers, including Oct4, Nanog, Sox2, and c-Myc.[29] Furthermore, it has been reported targeting Bmi-1 induces apoptosis via Noxa, a member of the BCL-2 family, in OSCC cell lines and *in vivo*.[30] Nevertheless, the specific underlying mechanisms by which PP7080 regulates EMT in OSCC require further elucidation.

The intricate interplay of autophagy, CSCs, and EMT is increasingly acknowledged in cancer progression, with autophagy exhibiting a complex, context-dependent role in both potentially suppressing early tumorigenesis and supporting survival in established tumors, particularly under stress such as hypoxia.[9] Our findings suggest a potential influence of PP7080 on this complex network, as evidenced by the reduced ABCG2 expression upon PP7080 knockdown. This observation may be relevant given the reported involvement of ABCG2 in autophagy-mediated drug resistance in breast cancer stem cells.[31,32] Furthermore, the co-expression and reported synergistic functions of ABCG2 and Bmi-1 in maintaining stemness and drug resistance[33] imply that PP7080's impact on both

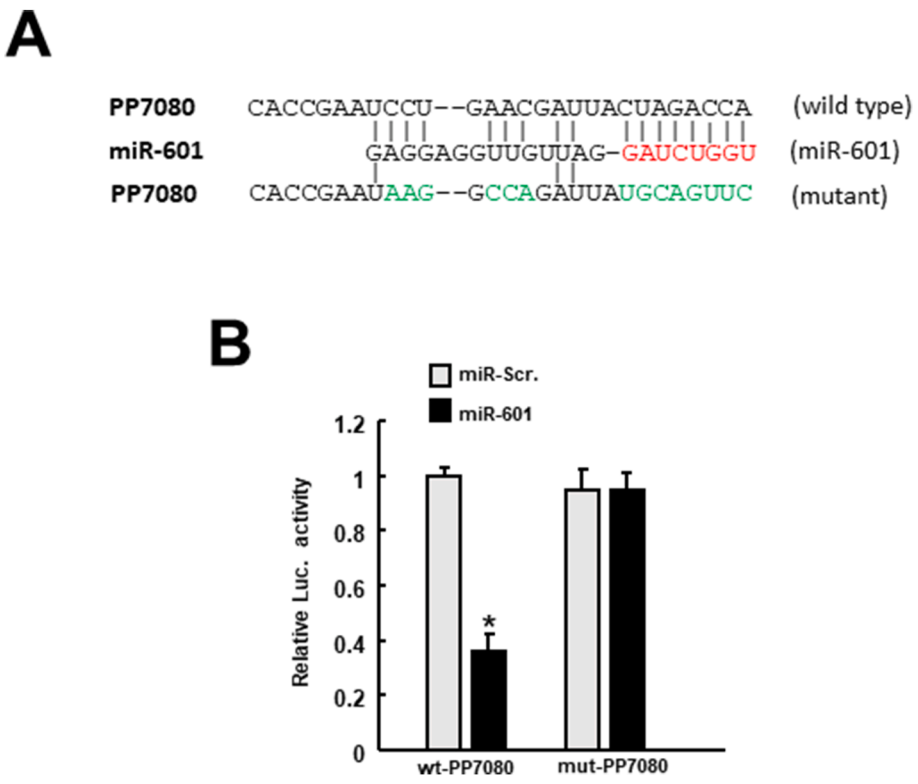

Figure 3 PP7080 directly interacts with miR-601. (A) Schematic representation of the predicted binding site of miR-601 on wild-type (wt) PP7080 and the mutated (mut) sequence in the luciferase reporter construct. (B) Relative luciferase activity in SAS cells co-transfected with reporters containing either wild-type or mutant PP7080 and either miR-601 or scrambled control (miR-Scr.). *$P < 0.05$ compared with miR-Scr. group for wt-PP7080.

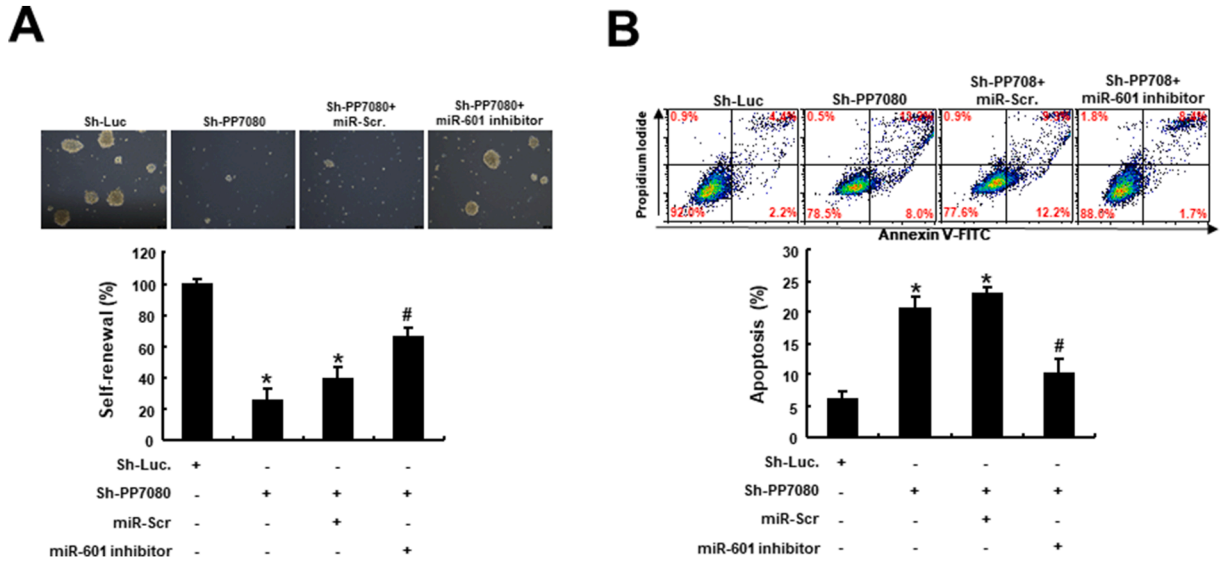

Figure 4 miR-601 inhibition partially rescues the effects of PP7080 silencing on self-renewal and survival. (A) Sphere-forming assay and (B) apoptosis analysis (Annexin V/PI staining) in Sh-PP7080 transfected SAS cells with or without miR-601 inhibitor. *$P < 0.05$ compared to Sh-Luc. group; #$P < 0.05$ compared with Sh-PP7080 group.

factors could contribute to its overall effect on the CSC phenotype. Given the involvement of Bmi-1 in autophagy-dependent cell death and its regulation of autophagy-dependent apoptosis in other cancer types,[34,35] our finding that PP7080 knockdown induced apoptosis while downregulating Bmi-1 highlights the complex interconnectedness of autophagy, CSCs, and EMT in OSCC progression.

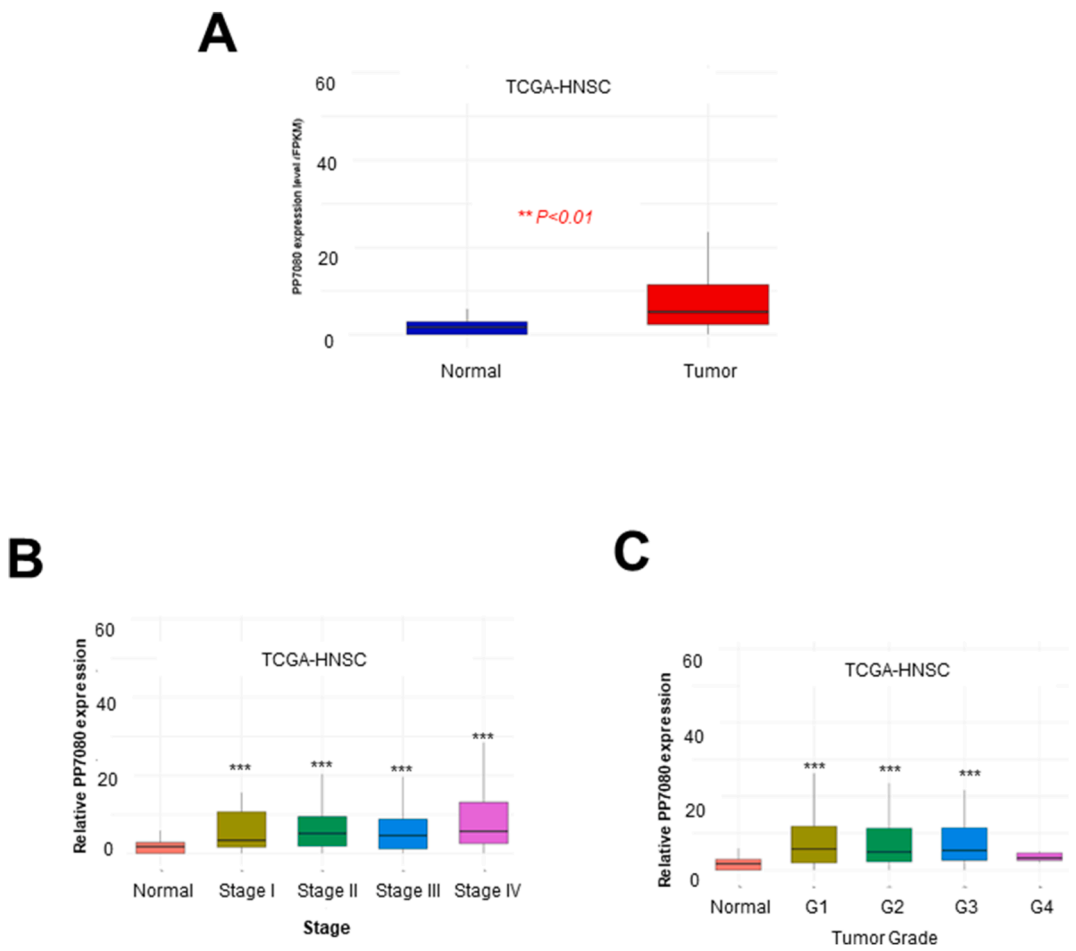

Figure 5 PP7080 is upregulated in HNSCC and correlates with stage and grade. (A) TCGA-HNSC analysis showed significantly higher PP7080 in Tumors vs. Normal, and across (B) tumor stages I-IV and (C) grades G1-G3. $^{**}P < 0.01$ compared with Normal group.

In conclusion, this study identifies lncRNA PP7080 as a key regulator of OSCC stemness. Further research is warranted to elucidate the precise molecular interactions among PP7080, miR-601, ABCG2, Bmi-1, and autophagy in OSCC, potentially revealing novel therapeutic targets.

Declaration of competing interest

All authors have no conflicts of interest relevant to this article.

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