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Original Article

SSTR2-targeting therapy in EBV-positive and EBV-negative metastatic nasopharyngeal carcinoma

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Abstract: Nasopharyngeal carcinoma (NPC) is an Epstein-Barr virus (EBV) - associated malignancy prevalent in South Asia, and somatostatin receptors (SSTRs), particularly SSTR2, are expressed in NPC and other solid tumors, suggesting a potential therapeutic target. We observed abundant SSTR2 expression in NPC cell lines and patient-derived xenografts (PDXs). In the EBV-negative PDX-Li41 model, treatment with the SSTR2 agonist octreotide (OCT) significantly inhibited xenograft growth and showed additive effects with chemotherapy; transcriptomic and protein analyses revealed heterogeneous regulation of cell-cycle-related genes, upregulation of DNA replication pathways, downregulation of cell-signaling and neurotransmitter-release pathways, and reduced expression of CDK6, NF-κB, E2F1, CDK2, and BIRC5. In contrast, OCT did not suppress tumor growth in the EBV-positive PDX-B13 model, prompting the development of an octreotide-monomethyl auristatin E (OCT-MMAE) peptide-drug conjugate, which demonstrated efficient cellular internalization, a low IC50 ($\approx 10^{-7}$ M), and significant inhibition of xenograft growth in both EBV-positive and EBV-negative PDX models. Evaluation of 118 metastatic NPC tumors showed that 91.5% were SSTR2-positive, and high SSTR2 expression was associated with significantly shorter overall survival ($P = 0.001768$), indicating that SSTR2 is widely expressed, linked to poor prognosis, and represents a promising therapeutic target in NPC.

Keywords: Nasopharyngeal carcinoma, Epstein Barr virus, SSTR2, patient derived xenograft, peptide-drug conjugate

Introduction

Metastatic NPC management

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy that is strongly associated with Epstein-Barr virus (EBV) infection and is highly prevalent in Southeast Asia [1]. According to the World Health Organization (WHO) classification, EBV is predominantly associated with type II non-keratinizing carcinoma and type III undifferentiated carcinoma, which together account for more than 90% of NPC cases in EBV-endemic regions [2]. Advances in diagnostic modalities, including quantitative plasma EBV DNA analysis, positron emission tomography-

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computed tomography (PET-CT), and magnetic resonance imaging (MRI), as well as therapeutic strategies such as concurrent chemoradiotherapy and intensity-modulated radiotherapy, have substantially improved the management of localized disease. However, distant metastasis remains a major challenge in NPC treatment [3].

For patients with recurrent or metastatic NPC, platinum-based doublet chemotherapy combined with anti-programmed death-1 (PD-1) monoclonal antibodies has become the predominant standard of care [4, 5]. In addition, emerging therapeutic approaches - including novel immunotherapies, therapeutic vaccines, adoptive cell therapies, bispecific antibodies, antibody-drug conjugates, and optimized supportive care - are showing promise for improving disease control in metastatic NPC [6].

SSTR2 in NPC

Somatostatin receptor 2 (SSTR2), a major subtype among the five somatostatin receptors (SSTR1-5), is a G protein-coupled cell surface receptor. Activation of SSTR2 by its endogenous ligand somatostatin (SS) or by somatostatin analogs (SSAs), such as octreotide (OCT), results in inhibition of intracellular signaling pathways, hormone secretion, and cell proliferation [7]. SSTR2 is highly expressed in neuroendocrine tumors (NETs), and SSTR2-targeted therapies - including SSAs and peptide receptor radionuclide therapy (PRRT) - have been widely applied in the clinical management of NETs [8]. PRRT employs radiolabeled SSAs, typically linking ^{177}Lutetium to OCT via a DOTA chelator, enabling selective targeting of SSTR2-expressing tumors through both receptor-mediated signaling modulation and localized radiotherapy [9]. In addition, ^{68}Ga-DOTA-OCT analogs have been used for imaging to detect SSTR2-expressing tumors, including NETs and NPC [10, 11]. Novel SSTR2-targeted agents, such as antibody- or peptide-based conjugates linked to cytotoxic drugs or radioisotopes, are currently under investigation for the treatment of SSTR2-expressing malignancies [12].

In NPC, SSTR2 has been reported to be highly expressed in primary tumors, recurrent lesions, and metastatic disease, and its expression has been associated with longer overall survival compared with tumors exhibiting low or absent SSTR2 expression [11].

Materials and methods

Drugs

Octreotide (OCT) was obtained from Novartis Pharma Stein AG (Stein, Switzerland). OCT-MMAE (Monomethyl auristatin E): MMAE-Suc-PEG8-Phe-Cys-Phe-Trp-Lys-Thr-Cys-Thr-Lys(MMAE-Suc)-Lys(MMAE-Suc)(Cys&Cys Bridge) and OCT-MMAE-FAM: MMAE-Suc-PEG8-Phe-Cys-Phe-Trp-Lys-Thr-Cys-Thr-Lys(MMAE-Suc)-Lys(5-FAM)(Cys&Cys Bridge) were synthesized by Mission Biotech Co., Ltd. (Taipei, Taiwan). Paclitaxel was purchased from Fresenius Kabi Oncology, Ltd. (Himachal Pradesh, India), and gemcitabine was purchased from TTY Biopharma Co., Ltd. (Zhongli, Taiwan).

Cancer cell lines and animal studies

Human cancer cell lines (C666-1) were purchased from the American Type Culture Collection (Manassas, VA, USA). The NPC-B13 cell line was generated from NPC PDX-B13 in our lab [13]. EBV-positive NPC cell lines (C666-1 and NPC-B13) and EBV-negative NPC cell line (HK-1) were maintained in RPMI containing 10% fetal bovine serum (FBS) and in DMEM/F-12 (Gibco, Thermo Fisher, MA, USA) supplemented with 10% FBS, respectively. SSTR mRNA, primers: sense: 5'-CATCATTGGGTTGTGTGCA-3', antisense: 5'-GCTCGATGCTCATGACTGTC-3'. Additionally, PDX animal studies were performed as described previously [13, 14]. Mice were maintained and handled in accordance with the Chang Gung Memorial Hospital (CGMH) Institutional Animal Care and Use Committee (IACUC) guidelines. All animal experiments were approved by the CGMH IACUC (IACUC No. 202212-2019).

Patient samples and SSTR2 immunohistochemistry staining

Clinical metastatic samples from 118 patients with NPC were retrospectively collected at CGMH between January 2007 and February 2024. This study was approved by the Institutional Review Board of CGMH (CGMH IRB No. 202101677B0). SSTR2 immunohistochemical staining in clinical tissue samples was quantified using the H-score method, calculated as follows: (3 × percentage of strong staining) + (2 × percentage of moderate staining) + (1 × percentage of weak staining), yielding a total score ranging from 0 to 300 [15].

PDX drug screening

The protocols for drug sensitivity tests have been previously described [14]. Briefly, NPC PDXs were implanted subcutaneously in the flank region of anesthetized NOD/SCID mice. Once the tumors reached a diameter of approximately 1 cm, treatment with various candidate chemicals was initiated simultaneously. Tumor dimensions were measured twice a week using calipers, and tumor volume was calculated using the formula: tumor volume (mm^3) = tumor length (mm) × [tumor width (mm)]^2 × 0.5. Tumors were then harvested for further analysis. Four to six mice per group (with or without chemical treatment) were used, and the mice were sacrificed 4-6 weeks after chemical injection.

Bulk RNA sequencing and differential expression gene analysis

Detail procedure had been described previously [16]. RNA was extracted from the cells as described previously. The raw fastq reads were aligned to a human-mouse-EBV hybrid reference genome by using the STAR software (GRCh38, GRCm39, and EBV-GD1 build). Furthermore, alignment quality was evaluated using Qualimap 2. The reads aligned to the mouse genome were removed prior to downstream analysis. Transcript abundance was evaluated using the STAR software with the default parameters. Additionally, the differentially expressed gene (DEG) analysis and gene ontology enrichment were performed as described previously. The EBV GD1 strain (GenBank accession no. AY961628) was chosen as the reference genome for sequence alignment and quantification. Gene counts were later converted to Reads Per Kilobase per Million mapped reads (RPKM) for DEG analysis.

Antibodies

The following antibodies were used in this study: SSTR2, ab134152 (Abcam, Cambridge, UK); cyclin D1, GTX61306 (Genetex, Hsinchu, Taiwan); CDK6, sc-7961 (Santa Cruz Biotechnology, Santa Cruz, CA, USA); p-RB, #9307 (Cell Signaling Technology, Danvers, MA, USA); NF-kB, #8242 (Cell Signaling Technology, Danvers, MA, USA); E2F1, #3742 (Cell Signaling Technology, Danvers, MA, USA); CDK2, sc-6248 (Santa Cruz Biotechnology, Santa Cruz, CA, USA); cyclin E2, #11935-AP (Proteintech, Chicago, IL, USA), BIRC5, #2808 (Cell Signaling Technology, Danvers, MA, USA); β-actin, sc-47778 (Santa Cruz Biotechnology, Santa Cruz, CA, USA); GAPDH, GTX100118 (Genetex, Hsinchu, Taiwan).

Statistical analysis

The median survival time of patients with NPC was estimated as the first observed event (death) at which the Kaplan-Meier survival probability was equal to 1.5. Furthermore, overall survival was calculated as the period from recurrence or metastasis to death, estimated by Kaplan-Meier plotting, and compared via log-rank test. Two-tailed *p*-values below 0.05 were considered statistically significant.

Results

SSTR2 expression in NPC PDX and cell lines

Previous studies have reported high SSTR2 expression in NPC tumors [11]. We therefore investigated SSTR2 expression in our NPC research models. Specifically, we assessed SSTR2 mRNA and protein expression in NPC patient-derived xenograft (PDX) models and cell lines. SSTR2 was abundantly expressed in approximately half of the NPC PDXs and cell lines examined and did not correlate with EBV status (**Figure 1A** and **1B**). Notably, immunohistochemical (IHC) staining revealed high SSTR2 expression in both NPC PDX-Li41 (EBV-negative) and PDX-B13 (EBV-positive) tumors (**Figure 1C**).

Octreotide inhibits tumor growth in PDX-Li41

We next evaluated the sensitivity of the SSTR2-targeting agent octreotide (OCT) in the PDX-Li41 model [16]. OCT treatment significantly inhibited PDX-Li41 tumor growth with potency comparable to the chemotherapeutic agent paclitaxel. Moreover, OCT exhibited an additive antitumor effect when combined with paclitaxel, as evidenced by reductions in tumor volume and final tumor weight, without affecting mouse body weight (**Figure 2**).

Transcriptomic and protein analyses

To elucidate the molecular mechanisms underlying OCT treatment, we performed transcriptomic analysis on OCT-treated PDX-Li41 tumors. OCT treatment was associated with differential

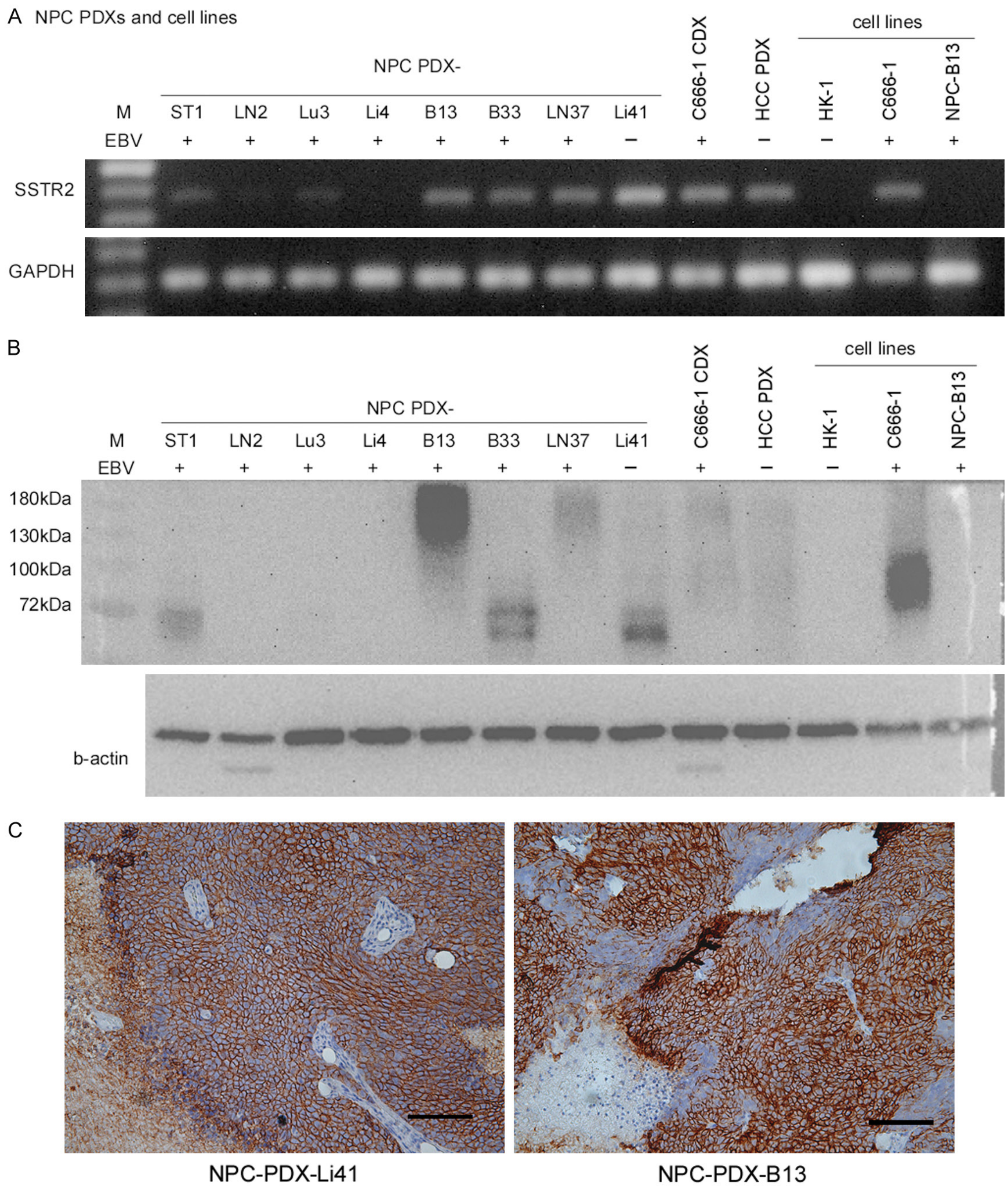

Figure 1. SSTR2 expression in NPC PDX models and cell lines. (A) SSTR2 mRNA expression and (B) protein expression in NPC patient-derived xenograft (PDX) models and cell lines. (C) Representative immunohistochemical (IHC) staining showing SSTR2 protein expression in NPC PDX tumors.

expression of genes involved in responses to external stimuli (**Figure 3A**). Additionally, OCT treatment was associated with upregulation of multiple cell cycle-related genes and DNA replication pathways, while concurrently suppressing cell-signaling pathways, including the NF-κB pathway, as well as neurotransmitter-release pathways (**Figure 3B**).

Changes in key protein expression following OCT treatment

We further validated changes in key protein expression following OCT treatment. Among the upregulated cell cycle-related genes identified by transcriptomic analysis, CDK6 - but not cyclin D1 - was reduced following OCT treat-

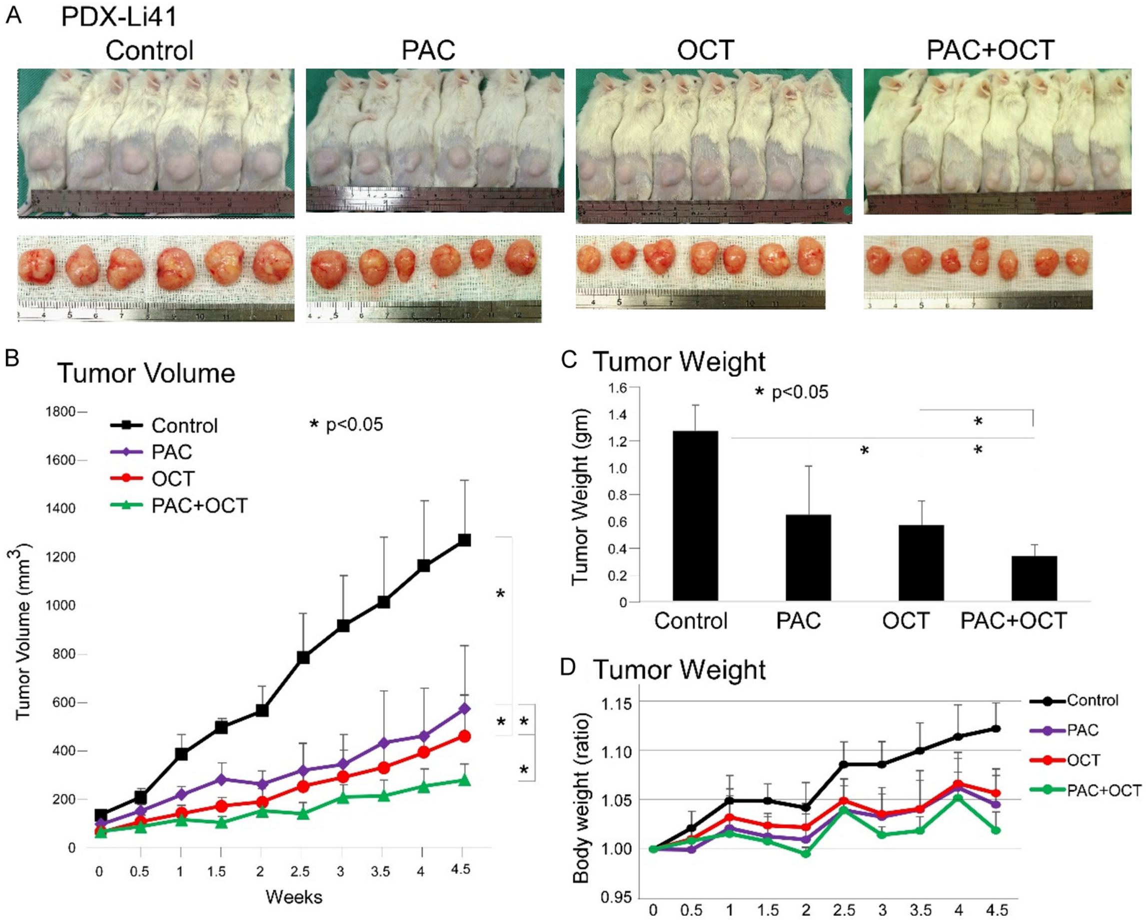

Figure 2. Antitumor effects of octreotide in the NPC PDX-Li41 model. NPC PDX-Li41 is an SSTR2-positive, EBV-negative PDX model. A. Representative gross tumor images. B. Tumor volume. C. Tumor weight. D. Mouse body weight during treatment. Abbreviations: PAC, paclitaxel; OCT, octreotide.

ment (**Figure 4A**). Other cell cycle regulators, including E2F1 and CDK2, were also downregulated. In addition, expression of BIRC5 (survivin), an inhibitor of apoptosis, as well as NF-κB, was suppressed (**Figure 4B**). Collectively, these findings suggest that OCT treatment modulates key regulators of the cell cycle, signal transduction, and apoptotic pathways.

Evaluation of OCT-MMAE in NPC PDX models

In our NPC PDX models, OCT did not inhibit tumor growth in the EBV-positive PDX-B13 model (**Figure 5A-C**). To enhance therapeutic efficacy, we synthesized a novel octreotide-monomethyl auristatin E conjugate (OCT-MMAE) and evaluated its anticancer activity in NPC cell lines and PDX models. Fluorescence-labeled OCT-MMAE (OCT-MMAE-FAM) demonstrated efficient cellular uptake in the NPC cell line C666-1 (**Figure 5D**). OCT-MMAE exhibited significantly greater cytotoxicity than OCT alone, with a low half-maximal inhibitory concentration (IC_{50}) of approximately 5-7 × 10^{-7} M in NPC cell lines (**Figure 5E**). In vivo, OCT-MMAE markedly inhibited tumor growth in both EBV-positive PDX-B13 (**Figure 5A-C**) and EBV-negative PDX-Li41 models (**Figure 5F-H**). These results indicate that the peptide-drug conjugate OCT-MMAE may represent a promising therapeutic candidate for NPC treatment.

SSTR2 expression in metastatic NPC tumors

We evaluated SSTR2 expression in metastatic NPC tumor samples (**Figure 6A**) obtained from Chang Gung Memorial Hospital, Linkou, Taiwan, collected between January 2005 and December 2023. A total of 118 metastatic tumor specimens were analyzed, of which 108 (91.5%) were positive for SSTR2 expression. Survival analysis revealed that patients with high SSTR2 expression (H-score ≥ 100) had significantly shorter overall survival compared with those

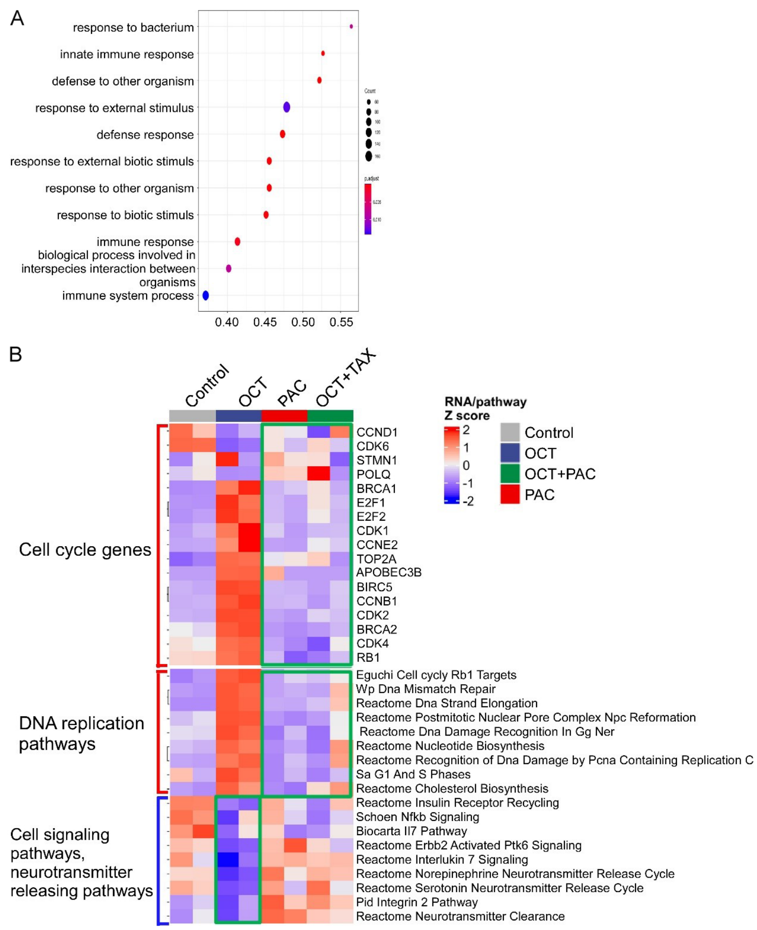

Figure 3. Transcriptomic analysis of octreotide treatment in NPC PDX-Li41. A. Differentially expressed genes associated with responses to external stimuli following octreotide (OCT) treatment in PDX-Li41 tumors. B. OCT treatment was associated with activation of cell cycle-related genes and DNA replication pathways, as well as suppression of cell-signaling pathways, including neurotransmitter-release pathways. Combined OCT and paclitaxel treatment further enhanced the activation of cell cycle-related genes and DNA replication pathways in PDX-Li41. Abbreviations: OCT, octreotide; TAX, paclitaxel.

with low SSTR2 expression (H-score < 100) (P = 0.001768; **Figure 6B**). These findings indicate that high SSTR2 expression is a poor prognostic factor in metastatic NPC.

Discussion

SSTR2 expression in NPC may not be exclusively induced by EBV

Somatostatin analogs (SSAs) have been established as standard therapies for advanced SSTR-positive neuroendocrine tumors (NETs) [17]. Clinical studies have demonstrated that SSAs achieve high rates of tumor growth control (50-80%) and prolonged survival in NET patients, although the objective response rate remains relatively low (< 10%) [17, 18]. The antitumor effects of SSAs are primarily mediated through hormone-suppressive mechanisms via inhibition of cyclic AMP signaling [19], as well as antiproliferative effects that include activation of phosphotyrosine phosphatases (PTPs) [20], induction of G1-phase cell cycle arrest [21], promotion of apoptosis [22], inhibition of angiogenesis [23], and immunomodulatory effects [24].

Previous studies have suggested that SSTR2 expression in NPC is induced by EBV through the LMP1-NF-κB signaling pathway, and SSTR2 has therefore been proposed as a surrogate biomarker for EBV-positive NPC [11]. However, the present study demonstrates that SSTR2 is highly expressed in both EBV-positive and EBV-negative metastatic NPC tumors. Notably, the EBV-negative NPC PDX-Li41 model was sensitive to octreotide (OCT) treatment, indicating that SSTR2 expression may be regulated by EBV-independent mechanisms and that SSTR2 represents a viable therapeutic target in metastatic NPC irrespective of EBV status.

In the EBV-negative PDX-Li41 model, OCT treatment was associated with downregulation of cell cycle-related genes, suppression of cell-signaling pathways, and inhibition of neurotransmitter-release pathways. These transcriptomic findings were corroborated at the protein level by reduced expression of CDK6, NF-κB, E2F1, and BIRC5 (**Figure 4**). Collectively, these results support the notion that activation of the SSTR2 signaling pathway can exert antitumor effects in EBV-negative metastatic NPC.

OCT-MMAE as a novel therapeutic candidate for metastatic NPC

Beyond SSAs, a variety of SSTR2-targeted therapeutic strategies - including conjugates of

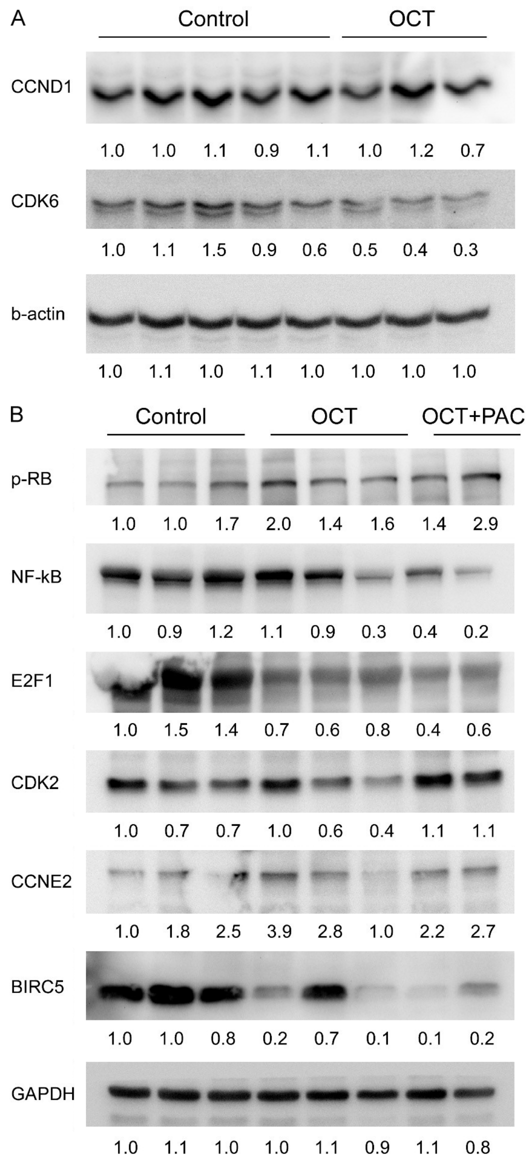

Figure 4. Changes in key protein expression following treatment in NPC PDX-Li41. A. Downregulation of selected cell cycle-related proteins following OCT treatment. B. Expression of key proteins before and after treatment with OCT alone or in combination with paclitaxel. Abbreviations: OCT, octreotide; PAC, paclitaxel.

anti-SSTR2 antibodies or SSAs linked to radionuclides or cytotoxic agents - have been developed for the treatment of SSTR2-overexpressing tumors, such as NETs, hepatocellular carcinoma, breast cancer, and small cell lung cancer [25-27].

Peptide receptor radionuclide therapy (PRRT), exemplified by ^177Lu-DOTATATE (Lutathera), has been established as a second- or third-line treatment for midgut NETs, demonstrating improved response rates and prolonged overall survival, with acceptable toxicity profiles [28, 29].

SSTR2 antibody conjugated to exatecan via a hydrophilic β-glucuronide linker, have shown high tumor control rates with low toxicity in NETs [30]. In recurrent or metastatic NPC, PEN-221 (SSA-DM1/mertansine), a peptide-drug conjugate distinct from OCT, has demonstrated tumor growth inhibition in preclinical models and is currently under clinical evaluation (NCT02936323) [11].

In the present study, we designed and characterized a novel SSTR2-targeting peptide-drug conjugate, OCT-MMAE. OCT-MMAE demonstrated efficient cellular uptake and potent cytotoxicity in NPC cell lines, with a low IC_{50} of approximately 10^{-7} M (**Figure 5C** and **5D**). Furthermore, OCT-MMAE markedly inhibited tumor growth in both EBV-positive and EBV-negative NPC PDX models (**Figure 5**). These findings suggest that OCT-MMAE is a promising therapeutic candidate for the treatment of SSTR2-expressing metastatic NPC.

SSTR2 as a poor prognostic factor in metastatic NPC

In head and neck squamous cell carcinoma (HNSCC), SSTR2 has been reported to be highly expressed in approximately 90% of EBV-positive NPC cases and has been proposed as a surrogate biomarker for this HNSCC subtype [31]. Earlier studies also reported that SSTR2 expression in primary, recurrent, and metastatic NPC tumors was associated with favorable prognosis [11]. However, more recent evidence suggests a more complex prognostic role for SSTR2 in NPC. High SSTR2 and/or EGFR expression in primary NPC has been associated with poorer survival outcomes and increased risk of disease progression, although such patients may derive benefit from combined chemoradiotherapy and EGFR-targeted therapy [32]. Additionally, elevated SSTR2 and/or PD-L1 expression has been linked to advanced disease stage, metastasis, tumor progression, and reduced survival [33]. Co-expression of SSTR2 and PD-L1 has also been observed, suggesting potential synergistic interactions in NPC pathogenesis and treatment response.

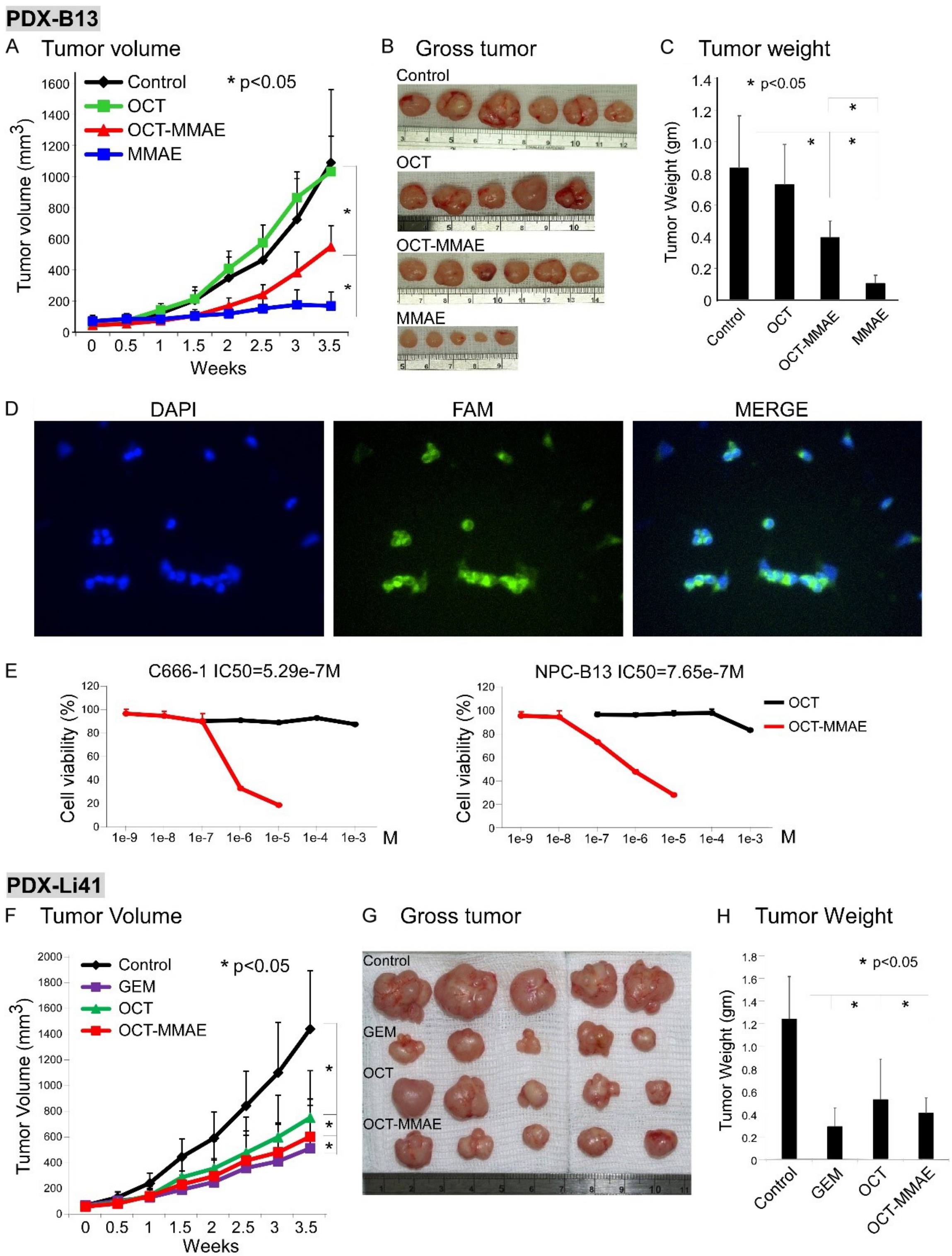

Figure 5. Antitumor efficacy of OCT-MMAE in EBV-positive and EBV-negative NPC PDX models. (A-C) EBV-positive PDX-B13: (A) tumor volume, (B) representative gross tumor images, and (C) tumor weight. (D) Cellular uptake of fluorescence-labeled OCT-MMAE (OCT-MMAE-FAM) in NPC cells. (E) Cytotoxicity of OCT-MMAE in NPC cell lines, shown as IC_{50} values. *Octreotide alone showed minimal cytotoxicity in NPC-B13 and C666-1 cells (IC_{50} > 10^{-4} M). (F-H) EBV-negative PDX-Li41: (F) tumor volume, (G) representative gross tumor images, and (H) tumor weight. Abbreviations: MMAE, monomethyl auristatin E; OCT, octreotide; OCT-MMAE, octreotide-monomethyl auristatin E.

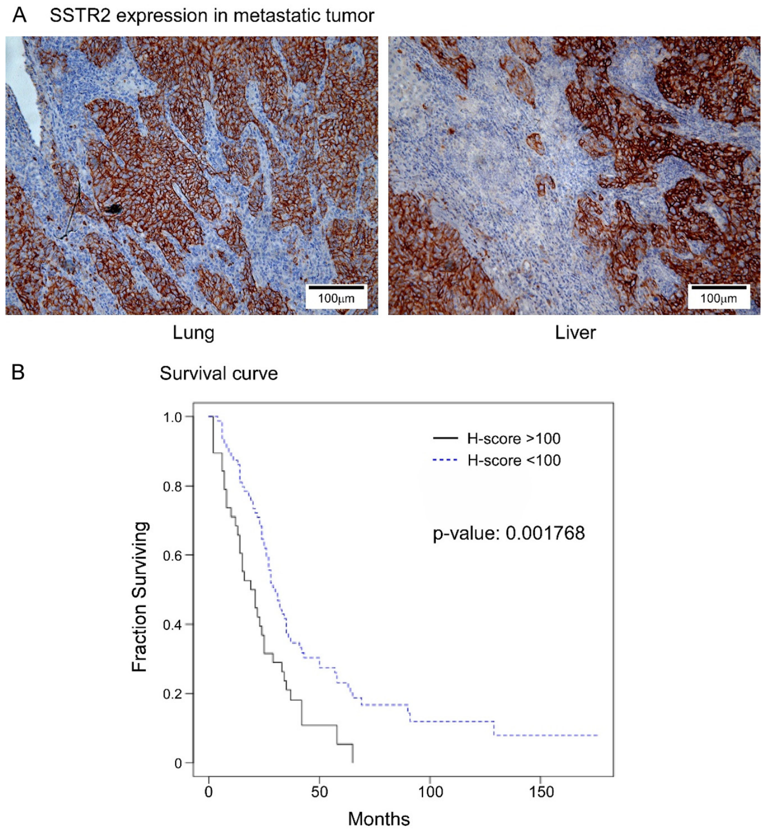

Figure 6. SSTR2 expression and clinical outcomes in metastatic NPC. A. Representative images showing high SSTR2 expression in metastatic NPC tumor samples. B. High SSTR2 expression is associated with shorter overall survival in patients with metastatic NPC.

Integrated next-generation sequencing and transcriptomic analyses have further demonstrated that SSTR2 is highly expressed in EBV-positive NPC and is associated with an inflamed and immunogenic tumor microenvironment [34]. Consistent with these emerging observations, the present study found that SSTR2 was expressed in 91.5% of metastatic NPC tumors and that high SSTR2 expression was significantly associated with shorter overall survival. These findings indicate that SSTR2 serves as a poor prognostic factor in metastatic NPC and highlight its potential value as both a biomarker and a therapeutic target in advanced disease.

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Disclosure of conflict of interest

None.

Abbreviations

DEG, differentially expressed gene; EBV, Epstein-Barr virus; EGFR, epithelial growth factor receptor; ICI, Immune checkpoint inhibitor; NPC, Nasopharyngeal carcinoma; NET, neuroendocrine tumor; NOD/SCID, non-obese diabetic mice with severe combined immunodeficiency; OCT, octreotide; OCT-MMAE, octreotide-monomethyl auristatin E; PD, programmed death; PDX, patient-derived xenograft; PDC, peptide-drug conjugate; PRRT, peptide receptor radionuclide therapy; SS, somatostatin; SSA, somatostatin analog; SSTR, Somatostatin receptor; WHO, World Health Organization.

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