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ORIGINAL ARTICLE

Prognostic value of histamine H1 receptor expression in oral squamous cell carcinoma

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Abstract
Objectives Overexpression of the histamine H1 receptor (H1R) has been described in a variety of tumor models, but experience in oral squamous cell carcinomas (OSCC) is not available. Current adjuvant treatment options for OSCC can be improved by the identification of new targets of therapy. Herein, we evaluated H1R expression in a large patient cohort of OSCC.
Materials and methods H1R immunoexpression was evaluated in 191 cases of OSCC and two OSCC cell lines BICR56 and BICR3. Scanned images were digitally analyzed using ImageJ and the immunomembrane plug-in. The combined score of computer-assisted semiquantitative analysis was correlated with manually counted percentages of tumor cells by Kendall's tau (τ) correlation coefficient. Disease-free survival times were estimated using the Kaplan–Meier method and were compared by using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model.
Results H1R was rarely expressed in OSCC but significantly related with advanced tumor stages (n=21/191, mean expression 63.5 % of cancer cells in positive tumor samples, 95 % confidence interval of the mean 53.5 to 73.6 %, p=0.006). Following univariate analysis, patients with H1R expression showed a significant poorer prognosis (p=0.0004). Multivariate analysis revealed H1R expression as an independent prognostic factor (p=0.0164). Expression of H1R in cancer cell lines was confirmed by specific staining of OSCC cell lines BICR56 and BICR3.
Conclusion This is the first study focusing on H1R expression showing a significant poorer DFS rate in the H1R+ patient cohort. Based on these data, H1R activation may promote carcinogenesis in OSCC.
Clinical relevance Investigation of H1R regulation and its antagonists shows a clear rationale for future supportive anticancer therapies in OSCCs.

Keywords Prognostic factors · Clinicopathological parameters · Oral squamous cell carcinoma · Histamine · Histamine 1 receptor

Introduction

A large number of molecules involved in cell proliferation and key events in tumor development and progression have been extensively investigated including histamine [1]. The hypothesis that histamine might be involved in carcinogenesis has been proposed in the 1960s, and it still remains under discussion today [2].

Histamine exerts its functions through binding to G protein-associated histamine H1, H2, H3, and H4 receptors (H1R, H2R, H3R, and H4R), resulting in activation of different signal transduction pathways [3]. Although many in vitro and in vivo studies of the modulatory roles of histamine in tumor development and metastasis have been reported, the effect of histamine in the progression of some types of tumors remains controversial. However, recent findings on the role of histamine in the immune system have shed new light on this question [3]. H1R and H2R were the

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first two histamine receptor subtypes described and thus the most frequently investigated in tumor cells and tissues. Until present, the distribution of histamine receptors in the carcinogenesis of oral squamous cell carcinoma (OSCC) is completely unknown.

The most important signal induced by H1R signalling is the activation of phospholipase C-generating inositol 1,4,5-triphosphate and 1,2-diacylglycerol leading to increased cytosolic calcium, which may exert pro-migratory effects on cancer cells. In addition to the inositol signalling system, H1R activation could lead to additional secondary signalling pathways. This rise in intracellular calcium levels seems to account for the various pharmacological activities promoted by the receptor, such as nitric oxide production, vasodilatation, liberation of arachidonic acid from phospholipids, and increased cyclic guanosine-3′,5′-monophosphate. Additionally, it was reported that H1R can directly increase the cyclic adenosine-3′,5′-monophosphate levels [4]. H1R also activates nuclear factor-kappaB (NF-kB) through Gαq11 and Gβγ upon agonist binding, while constitutive activation of NF-kB occurs only through the Gβγ [5, 6]. Recently, it was reported that the stimulation of H1R induced H1R gene expression through protein kinase C δ activation results in receptor upregulation [7]. Summarizing, H1R activation may promote carcinogenesis by inflammatory stimuli leading to nitric oxide production, liberation of arachidonic acid from phospholipids, and activation of NF-kB [3, 8].

Although many in vitro and in vivo studies on the modulatory roles of histamine in tumor development and metastasis have been reported, the effect of histamine in the progression of some types of tumors remains controversial. In this respect, it was previously found that histamine stimulates melanoma cell growth and that H1 histamine receptor antagonists induce apoptosis in a variety of human melanoma cell lines [9, 10]. The in vitro usage of H1R antagonists (terfenadine and loratadine), respectively suppresses proliferation of cancer cells making them attractive as anticancer agents [9–17] in human leukemia, myeloma [16, 17], colon, and liver cancer cells [18]. In this context, investigation of H1R and its antagonists shows a clear rationale for future supportive anticancer therapies. Therefore, the aim of this study is measurement of H1R expression in patients with OSCC in association with clinicopathological prognostic factors and disease-free survival (DFS) rates.

Materials and methods

Patients and tumor specimen

We retrospectively reviewed the records of 191 patients after primary radical R0 tumor resection in our department over a period of 10 years. Patients with nonresectable disease, inadequate follow-up data, and patients with preoperative antineoplastic therapies (chemoradiation/chemotherapy) were excluded from the study. The diagnosis of squamous cell carcinoma was confirmed by the Department of Pathology, University Hospital Tuebingen, and the specimens were retrieved retrospectively from the pathology archives. The material was archival formalin-fixed, paraffin-embedded (FFPE) tissue from routine histopathologic work-up. The study was approved by the local ethics committee. Informed consent was obtained from the patients prior to surgical resection. Follow-up data were obtained from our local tumor registry. The last follow-up was recorded from the last outpatient visit or the date of locoregional recurrence or tumor-specific death, respectively. Tumor and patient characteristics are summarized in Table 1.

Tumor blocks of paraffin-embedded tissue were selected by experienced pathologists, evaluating the routine H.E.-stained sections. Sections from all available tumors underwent intensive histopathologic assessment, blinded to the prior histopathology report. Serial tissue sections (2 μm thickness) were cut from FFPE blocks on a microtome and mounted from warm water onto adhesive microscope slides. Tumor staging was performed according to the 7th edition of the TNM staging system by the International Union Against Cancer (UICC)/AJCC of 2010 [19]. Grading was performed according to WHO criteria [20]. Tumor characteristics (UICC stage, pT categories, pN categories, cM categories, infiltrated lymph nodes, residual tumor status, tumor size, and site distribution) and patient characteristics (gender, age, personal history, and habitual history) were collected in a database (Excel, Microsoft). Surgical margin status was determined on final histopathologic evaluation. Close margins were deemed positive in all analyses, whereas negative margins were considered greater than or equal to 10 mm from resection margin after tissue fixation.

Staining procedure and quantification of immunohistochemistry

For immunohistochemical analysis, specific H1R and isotype control antibodies were purchased from from Santa Cruz (Heidelberg, Germany, specific H1R clone H-20: sc-19767, dilution: 1:50). Processing of tissue, pretreatment (fixation, deparaffinization, rehydration, heat-induced epitope retrieval of FFPE slides, and blocking), and staining procedure were performed as described earlier [21]. Quantification of immunohistochemistry was done by means of cell counting. The results were expressed as percentages (number of positive tumor cells within 100 counted tumor cells, [21]). Moreover, for computer-assisted semiquantitative analysis of H1R expression, ImageJ software (http:/rsbweb.nih.gov/ij/) coupled with immunomembrane plug-in (http://imtmicroscope.uta.fi/immunomembrane) was used to assess the quantification of H1R immunoreactivity

Table 1 Clinicopathological characteristics and prognostic factors of 191 patients with OSCC

Characteristics	Total n=191	Number of patients		*p* value
		Histamine H1 receptor expression negative, *n*=170 (89 %)	Histamine H1 receptor expression positive, *n*=21 (11 %)	
Age (years)				0.9351
<62	103 (53.9 %)	92 (89 %)	11 (11 %)	
≥62	88 (46.1 %)	78 (89 %)	10 (11 %)	
Gender				0.3995
Male	145 (75.9 %)	127 (88 %)	18 (12 %)	
Female	46 (24.1 %)	43 (93 %)	3 (7 %)	
Site distribution of OSCC				0.6726
Lips	11 (5.8 %)	11 (100 %)	0 (0 %)	
Tongue	42 (22.0 %)	37 (88 %)	5 (12 %)	
Floor of the mouth	84 (44.0 %)	76 (90 %)	8 (10 %)	
Palate	17 (8.9 %)	14 (82 %)	3 (18 %)	
Buccal mucosa	10 (5.2 %)	8 (80 %)	2 (20 %)	
Alveolar ridge	27 (14.1 %)	24 (89 %)	3 (11 %)	
Histological grading				0.5362[a]
G1	50 (26.2 %)	46 (92 %)	4 (8 %)	
G2	125 (65.4 %)	111 (89 %)	14 (11 %)	
G3	15 (7.9 %)	12 (80 %)	3 (20 %)	
G4	1 (0.5 %)	1 (100 %)	0 (0 %)	
Depth of invasion				0.0015[b]
pT1	75 (39.3 %)	73 (97 %)	2 (3 %)	
pT2	52 (27.2 %)	47 (90 %)	5 (10 %)	
pT3	18 (9.4 %)	13 (72 %)	5 (28 %)	
pT4	46 (24.1 %)	37 (80 %)	9 (20 %)	
Cervical lymph node metastasis				0.0021
pN0	133 (69.6 %)	125 (94 %)	8 (6 %)	
pN1-3	58 (30.4 %)	45 (78 %)	13 (22 %)	
UICC stage				0.006[c]
UICC I	57 (29.8 %)	55 (96 %)	2 (4 %)	
UICC II	42 (22.0 %)	41 (98 %)	1 (2 %)	
UICC III	34 (17.8 %)	26 (76 %)	8 (24 %)	
UICC IV	58 (30.4 %)	48 (83 %)	10 (17 %)	
Locoregional recurrence				0.1304
No	140 (73.3 %)	128 (91 %)	12 (9 %)	
Yes	51 (26.7 %)	42 (82 %)	9 (18 %)	

G grading, *UICC* International Union Against Cancer

[a]G1/2 vs. G3/4

[b]pT1/2 vs. pT3/4

[c]UICC I/II vs. UICC III/IV

in microscopically acquired JPEG images of OSCC samples. Staining completeness (0–10 points) and intensity (0–10 points) were added for a combined score (0–20 points). From H1R-positive slides, five images per sample showing representative tumor areas were acquired using 10× and 20× objectives to assess precision (reproducibility/repeatability) of computer-assisted semiquantitative analysis.

Cell culture

We analysed H1R expression in cells (1×10^4) from the OSCC cell lines BICR3 and BICR56 (American Type Culture Collection) in cytospins as a positive control of H1R expression by cancer cells. Preparation and staining of cytospins was performed as described before [22]. BICR3 and

BICR56 cells were cultured in DMEM F-12 medium (Invitrogen, Belgium) containing 10 % FCS (Sigma-Aldrich, Germany) and 1 % fungicide and penicillin/streptomycin (Biochrom, Germany) at 37 °C and 5 % CO_2.

Statistical analysis

Statistical analysis was performed with MedCalc Software, version 12.2.1 (Mariakerke, Belgium). DFS was calculated from the time of tumor resection until obvious locoregional recurrence or tumor conditional death, respectively. To analyze differences in the DFS among patients after successful (R0) curative surgical resection for OSCC, patients were divided into H1R positive (H1R+) and H1R negative (H1R−) subgroups (dichotomous variables). The DFS times were estimated using the Kaplan–Meier method [23] and were compared by using the log-rank test [24]. Multivariate analyses were performed using the Cox proportional hazards model [25]. All parameters that were found significant on univariate analysis were included. Hazard ratios (HR) for variables that may influence survival status in univariate and multivariate analysis were provided with 95 % confidence interval (CI). Chi-square test (χ^2) and Fisher's exact test were used to investigate the relation between two categorical variables. Kendall's tau (τ) correlation coefficient was measured to assess the accuracy (the degree of closeness of measurements of a quantity to that quantity's actual value) between the two quantification methods of immunohistochemical analysis (manually counted percentages of positive tumor cells within 100 counted tumor cells vs. combined score of computer-assisted semiquantitative analysis). All p values presented were two-sided, and $p<0.05$ was considered statistically significant.

Results

A preliminary study was carried out to assess the accuracy between the two quantification methods of immunohistochemical analysis. There were significant correlations between the first (manually counted percentages of positive tumor cells within 100 counted tumor cells) and the second (combined score of computer-assisted semiquantitative analysis) assessment: H1R expression: τ=0.990, $p<0.0001$, 95 % CI 0.981 to 0.998.

H1R expression is associated with tumor progression of OSCC

H1R was not expressed in normal oral squamous epithelium. H1R expression in stromal cells was considerably weak, but it was strongly associated with cancer cells. Eleven percent (n=21/191) of the patients with OSCC expressed H1R within the tumor. Table 1 shows clinicopathological characteristics and prognostic factors of 191 patients with OSCC. H1R expression (n=21/191, mean expression 63.5 % of cancer cells in positive tumor samples, 95 % CI for the mean 53.5 to 73.6 %) was significantly associated with depth of invasion (pT3/4, p=0.0015), cervical lymph node metastasis (pN1-3, p=0.0021), and advanced tumor stages (UICC III/IV, p=0.006). Immunohistochemistry of serial sections shows representative images of IgG control and H1R expression in OSCC (Fig. 1a–f). Staining of the OSCC cell lines BICR56 and BICR3 in cytospins served as an additional positive control and showed a different expression pattern for H1R expression (Fig. 2a–c). Eighty to ninety percent BICR56 cells stained positively for H1R expression, whereas only fewer than 5 % BICR3 showed specific H1R staining.

Prognostic value of H1R expression in OSCC

To analyze survival rates in patients after successful (R0) curative surgical resection of OSCC, patients were divided into two subgroups as described above (dichotomous variables). Cervical lymph node metastasis (pN1-3, $p<0.0138$, HR=2.0010, 95 % CI=1.0411 to 3.8458) was shown to be an unfavorable factor in univariate analysis of all (n=191) OSCCs. Depth of invasion (pT3/4, $p<0.1903$, HR=1.4689, 95 % CI=0.7706 to 2.7999) and grading (G3/4, $p<0.8052$, HR=0.8641, 95 % CI=0.2893 to 2.5813) were not found to be unfavorable factors in univariate analysis.

To analyze differences in tumor-related survival dependent on H1R expression in OSCC, we divided the patients into two subgroups as described above (dichotomous variables). Survival in subgroup with positive H1R expression (H1R+) in OSCC (n=21, p=0.0004, HR=3.3645, 95 % CI=1.0581 to 10.6982) was significantly worse in comparison to the subgroup of patients failing H1R expression (Fig. 3a, interrupted versus black line).

Multivariate analysis using the Cox proportional hazards model demonstrated positive H1R expression (H1R+) but not lymph node metastases as independent prognostic factors in all (n=191) OSCC (H1R+: Exp (b) 2.6825; 95 % CI of Exp (b) 1.2035 to 5.9791; p=0.0164. LN positive, pN1-3: Exp (b) 1.5777; 95 % CI of Exp (b) 0.8421 to 2.9559; p=0.1567; Fig. 3b).

Discussion

In this hospital-based study, samples of 191 patients with oral cavity squamous cell carcinoma treated by primary surgical resection were analyzed regarding the coherence of H1R expression and subsequent survival rates. This is the first study focusing on H1R expression that might serve as an extension to clinicopathological parameters for

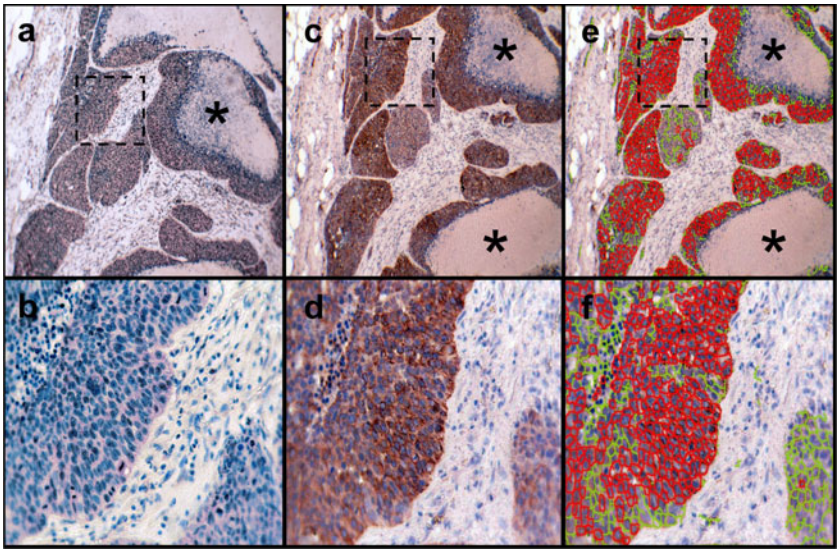

Fig. 1 Immunohistochemical staining of serial sections shows representative images of IgG control (**a**, **b**) and H1R expression (**c**–**f**) in OSCC (membranous staining pattern, *brown*). IgG control (**a**, **b**) shows no staining. Pseudo-colored images (**e**, **f**) show the staining components of computer-assisted semiquantitative analysis in H1R+ OSCC cells (**c**, **d**). *Red label* indicates strong or complete staining. *Green label* indicates weak or incomplete staining, the *brown color* indicates positive H1R staining, and the *blue color* indicates the nuclear counterstaining by hematoxylin. *Asterisks* show areas of tumor necrosis. The *square box* demonstrates the area of interest (original magnification: ×100-fold, *upper panel*) which is also shown in larger magnification (×200-fold, *lower panel*)

prognosis and treatment with OSCC. We found H1R expression as an independent prognostic factor for DFS in our patient cohort. However, only a small number of tumor samples (21 out of 191 patients) stained positively for H1R expression identifying H1R expression as an exceptional case

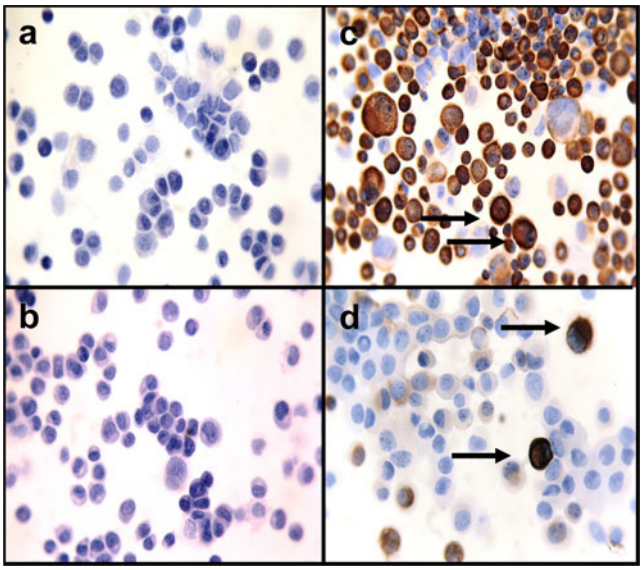

Fig. 2 Immunohistochemical staining of H1R expression in BICR3 and BICR56 OSCC cell lines. The negative control (IgG control) (**a** BICR3; **b** BICR56) shows no staining. H1R specific staining (membranous staining pattern, *brown color*) in cytospins serves as positive control for H1R expression by cancer cell lines and shows 80–90 % positive cells in BICR56 (**c**), whereas BICR3 (**d**) staining reveals very few (<5 %) positive cancer cells (*arrows*). Original magnification: ×400-fold

but important factor for carcinogenesis in OSCC. Suggestions for the regulation of H1R expression have been reviewed by Miyoshi et al. [26]. Medication therapies including beta-2 receptor agonists (e.g., salbutamol, salmeterol, and formoterol), muscarinic receptor (M3R) antagonists (e.g., ipratropium and tiotropium), steroids, and H1R signal transduction antagonists may influence expression levels of H1R and therefore potentially impact further tumor progression. A complete summary of the medication of each patient was not available for further associations in this context, but H1R expression seems to be relevant for future prospective clinical trials. In this context, agonists of M3R, H1R and protein kinase C signalling pathways [26], mediated by other G protein-coupled receptors (e.g., prostaglandin E2 receptor) in the inflammatory microenvironment of tumors [8] and retinoic acid [27] were described to promote tumor growth. The reason for H1R upregulation in selective cases of OSCC remains an enigma, but we hypothesize that once activated, H1R expression levels increase within the tumor based on reasons (e.g., H1R signal regulation by itself or medications from underlying diseases) mentioned above. This suggestion is supported by our data of mean expression levels in H1R-positive tumor samples.

Selective activation of the H1R has been shown to produce, respectively, inhibition or stimulation of tumor growth in a dose-dependent manner. In a number of experimental tumor models [15, 28–31], H1R activation has been correlated with inhibition of cell growth (G0/G1 cell cycle arrest)

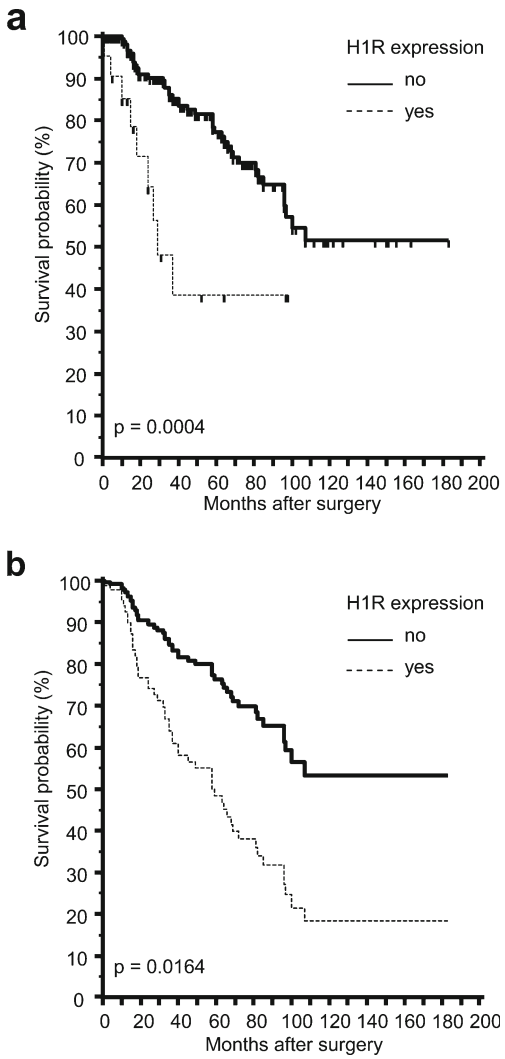

Fig. 3 Kaplan–Meier (**a**) and Cox regression (**b**) survival curves for disease-free survival (DFS) stratified by positive (H1R+, *dashed line*) and negative (H1R−, *solid line*) H1R staining. H1R expression (n=21/191) in OSCC is found to be associated with poorer survival. DFS 1-, 3-, and 5-year survival rates (H1R+ vs. H1R−) in univariate Kaplan–Meier survival curve (**a**) are 98 vs. 85 %, 86 vs. 48 %, and 77 vs. 38 %, respectively. DFS 1-, 3-, and 5-year survival rates (H1R+ vs. H1R−) in multivariate Cox-regression (**b**) survival curve are 96 vs. 90 %, 84 vs. 64 %, and 77 vs. 48 %, respectively. The times of the censored data are indicated by *short vertical line*

[12, 32]. Based on our results, we suggest also the support of chronic inflammation (e.g., activation of NF-kB, [3, 8]) in the tumor microenvironment mediated by H1R signalling rather than a cell cycle arrest of OSCC tumor cells. Our data of significant poorer DFS rate in the H1R+ patient cohort and association with the clinicopathological analysis support this hypothesis. However, a previous study showed evidence for decreased expression rates of H1R in colorectal carcinoma [33].

The current knowledge about the role of histamine in carcinogenesis is complex. The endogenous activity of histidine decarboxylase (the only enzyme responsible for the generation of histamine from L-histidine) in tumor cells and tumor-infiltrating mast cells is likely to establish an autocrine loop in which histamine acts as a growth factor [28–31]. Paradoxically, the exogenous administration of histamine at higher concentrations seems to exert antitumoral properties through both direct and indirect effects on tumor cells [34]. However, the expression patterns of the four histamine receptors in OSCCs and their regulatory pathways induced by their activation have to be better elucidated before histamine or its receptor agonists/antagonists can be definitively proposed as new anticancer agents [35, 36].

Conclusions

In conclusion, this is the first study focusing on H1R expression showing significant poorer DFS rates in the H1R+ patient cohort. Based on these data, H1R activation may promote carcinogenesis in OSCC. Investigation of H1R regulation and its antagonists shows a clear rationale for future supportive anticancer therapies in OSCCs.

Competing interests The authors declare that they have no conflict of interest.

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