Journal of Cancer Research and Clinical Oncology (2025) 151:103
https://doi.org/10.1007/s00432-025-06154-5

RESEARCH

Semaglutide, a glucagon-like peptide-1 receptor agonist, inhibits oral squamous cell carcinoma growth through P38 MAPK signaling pathway

Can Wang[1,2] · Zhengzheng Wu[1,2] · Jiaying Zhou[1,2] · Bin Cheng[1,2] · Yulei Huang[1,2]

Received: 6 February 2025 / Accepted: 26 February 2025

Abstract

Aims Researches have shown that diabetes mellitus (DM) can promote the risk and progression of oral squamous cell carcinoma (OSCC). Semaglutide, a glucagon-like peptide-1 receptor agonist, is currently employed to treat type 2 diabetes mellitus (T2DM) and obesity. This study intends to explore the potential effects and mechanism of Semaglutide on OSCC.

Methods The expression of GLP-1R in OSCC cells and tissues was evaluated by qRT-PCR, western blot and immunohistochemistry assays. Cell proliferation, invasion, migration and apoptosis abilities were determined by relevant experiments. Western blot was employed to verify the expression of relevant proteins and examine the effect of Semaglutide on the MAPK signaling pathway. The xenograft transplantation model of OSCC was established to examine the anti-cancer effects of Semaglutide in vivo and immunohistochemistry assays were performed on tumor tissues.

Results GLP-1R expression was elevated in OSCC cells and tissues as compared with that in normal. Semaglutide effectively inhibited the proliferation, migration and invasion of OSCC cells while concurrently promoting apoptosis. Moreover, Semaglutide specifically activated the P38 MAPK signaling pathway without significant influence on ERK1/2 or SAPK/JNK, and its pro-apoptotic effects in OSCC cells was related to P38 pathway activation. Animal experiments verified the inhibitory effect of Semaglutide on OSCC tumors in mice.

Conclusions Semaglutide exerts inhibitory actions on OSCC and may induce apoptosis in OSCC cells via the P38 MAPK signaling pathway. This study has significant implications for the treatment of patients with diabetes who are also afflicted by OSCC.

Keywords GLP-1R · Semaglutide · OSCC · P38 MAPK signaling pathway

Introduction

As the sixth most prevalent cancer globally and the second leading cause of cancer-related fatalities worldwide, oral cancer has emerged as an increasingly serious global health problem (Ramos-Garcia et al. 2021; Li et al. 2024a, b). Oral squamous cell carcinoma (OSCC) is the predominant type of oral cancer, accounting for approximately 90% of cases. It is particularly prevalent in low- and middle-income countries, with high morbidity and mortality rates (Suri et al. 2024). Diabetes mellitus (DM) is also a major global health concern. Currently, approximately 537 million adults are afflicted with diabetes, and this number is expected to rise to 783 million by the year 2045 (Ahmad et al. 2022). Studies have revealed that individuals with DM possess a higher propensity to develop oral cancer and a greater risk of mortality compared with nondiabetics. The prevalence of DM

✉ Bin Cheng
chengbin@mail.sysu.edu.cn

✉ Yulei Huang
huangyulei@mail.sysu.edu.cn

Can Wang
wangc75@mail2.sysu.edu.cn

Zhengzheng Wu
wuzhzh23@mail2.sysu.edu.cn

Jiaying Zhou
zhoujy63@mail2.sysu.edu.cn

[1] Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, Guangzhou 510055, People's Republic of China

[2] Guangdong Provincial Key Laboratory of Stomatology, Guangzhou 510080, People's Republic of China

Published online: 07 March 2025

in patients diagnosed with oral cancer is also significantly higher than that observed in patients without oral cancer (Ramos-Garcia et al. 2021; Vegh et al. 2022). Moreover, Hu et al. found that compared with OSCC cells cultured with low glucose concentration (1 g/L), OSCC cells cultured with high glucose concentration (4.5 g/L) showed higher proliferation, migration, invasion level and lower apoptosis rate. They proposed that T2DM may influence the progression of OSCC through hyperglycemia (Hu et al. 2022). Collectively, these findings suggest some correlation between DM and OSCC.

The glucagon-like peptide-1 receptor (GLP-1R), a member of the G protein-coupled receptor (GPCR) family, is expressed in multiple tissues, including the pancreas, lung, liver, kidney, stomach, intestine, heart, and central nervous system regions (Ibrahim et al. 2024; Zheng et al. 2024). GLP-1, an incretin hormone, is rapidly released 15–30 min subsequent to nutrient intake and acts on GLP-1R to enhance insulin biosynthesis and secretion while inhibiting glucagon release from the pancreas (Holst and Gromada 2004; Sharma et al. 2018). In addition, GLP-1 provides neuroprotective effects and alleviates inflammation in the brain (Verma and Goyal 2024). Due to the short half-life of GLP-1, several GLP-1 analogs have been developed to act as GLP-1R agonists (GLP-1RAs), which exert the same effects as endogenous GLP-1 and are currently predominantly utilized to treat type 2 diabetes (T2DM) (Ma et al. 2021; Zhao et al. 2021; Pandey et al. 2023). With the use of GLP-1RAs, concerns have arisen regarding their potential relationship with cancer risk. Presently, some studies have explored the correlation between GLP-1RAs and several types of malignancies, such as thyroid cancer, pancreatic cancer, colorectal cancer, breast cancer, and other tumor diseases. However, the conclusions are not entirely consistent. Some researches indicate that GLP-1RAs may facilitate the occurrence and progression of tumors; conversely, other studies report opposite results or identify no significant association between GLP-1RAs and tumors (Koehler et al. 2011; Chen et al. 2013; Zhao et al. 2014, 2021; Azoulay et al. 2016; Iwaya et al. 2017; Piccoli et al. 2021; Ueda et al. 2021; Tong et al. 2022; Ji et al. 2024). Nevertheless, whether a linkage exists between GLP-1RAs and OSCC remains unclear.

Semaglutide is a GLP-1R agonist, which is highly derived from natural human GLP-1 but has a long half-life. It can reduce medication frequency and improve patient adherence and is currently mainly used in the treatment of T2DM and obesity (Andreadis et al. 2018; Dhillon 2018; Chao et al. 2023). Semaglutide is the only GLP-1RA available for the management of T2DM in both injection and oral dosage forms (Marassi and Fadini 2025). Compared with other GLP-1RAs, Semaglutide demonstrates superior blood sugar control and weight loss, as well as a lower risk of cardiovascular mortality and more benefits for the kidneys (Sorli et al. 2017; Capehorn et al. 2020; ElSayed et al. 2023; Hu et al. 2024). Furthermore, a recent meta-analysis involving 37 studies with a total of 46,719 patients concluded that the utilization of Semaglutide did not increase any cancer risk (Nagendra et al. 2023). At present, there is a deficiency of research regarding the effect of Semaglutide on OSCC. Consequently, we explored the role of Semaglutide on OSCC through in vivo and in vitro studies.

The development of OSCC involved multiple molecular signaling networks, among which the MAPK signaling pathway plays an important role in tumor progression (Huang et al. 2024). Mitogen-activated protein kinases (MAPKs), including P38, ERK1/2, and SAPK/JNK, are associated with crucial biological processes such as cell proliferation, differentiation, and apoptosis, and exert profound effects on the development of OSCC(Dhillon et al. 2007). In order to further explore the mechanism of the effect of Semaglutide on OSCC, we detected the key molecules of MAPK pathway in this study.

Materials and methods

Primary tumor studies

Primary tumor specimens were obtained from the Department of Pathology at the Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University (Guangzhou, China). 10 OSCC tissues and 10 matched normal oral epithelial tissues were included.

Cell studies

(1) Cells culture

CFPAC-1 cells, NOK cells, and OSCC cell lines were maintained in our laboratory in Guangzhou, which were purchased or donated from reliable authorities. The two main cell lines used in this study, Cal27 and HSC4, were authenticated by STR profiling. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, USA).

(2) CCK-8 assays

Cal27 or HSC4 cells were prepared into cell suspension, and 3000 cells per well were seeded in 96-well plates (Corning, USA). After attachment, cells were cultured with 0, 5, 10, 20, or 40 μmol/L Semaglutide (Novo Nordisk, Switzerland) for 24 h, or 0 or 5 μmol/L Semaglutide for 96 h. The concentrations of Semaglutide in this study were selected based on

pre-experiment and previous literature (Eftekhari et al. 2020; Zhu et al. 2021). CCK-8 solution (10 µL/ well) was added and allowed to incubate in darkness within an incubator for 2 h every 24 h, and the optical density (OD) values were then measured at 450 nm using a microplate reader (Biotek, USA).

(3) IncuCyte S3 Platform

Cal27 or HSC4 cells (3×10^3) were seeded in a 96-well plate and subsequently treated with 0, 5, 10, 20 or 40 µmol/L Semaglutide. Phase contrast images of the cells were captured using a 4×objective lens every 12 h over a total duration of 72 h with an IncuCyte S3 Live Cell Analysis System (Sartorius, Germany). IncuCyte S3 image analysis software was set to assess the confluence in the percentage of the cells, and the proliferation rate was determined as the area confluence ratio normalized against the baseline (time 0 after Semaglutide was added).

(4) Colony formation assays

Cal27 or HSC4 cells (1×10^3) were plated in 6-well plates and cultivated with varying concentrations of Semaglutide (0, 5, or 10 µmol/L) for 14 days. The culture medium was refreshed every three days. After that, the colonies were rinsed with phosphate-buffered saline (PBS; Gibco, USA), fixed in 4% paraformaldehyde (PFA; Servicebio, China) for 15 min, and then stained with 0.1% crystal violet for an additional 15 min. Images were captured using a photo scanner (Epson, Tokyo).

(5) Wound healing assays

Cal27 or HSC4 cells (4×10^5) were seeded in a 6-well plate until 90% confluency and allowed to form a confluent monolayer. A 1 mL tip was then used to create a scratch within the cell layer. Following this, the cells were washed twice with PBS to eliminate detached cells and subsequently replaced with serum-free medium containing 0, 5, or 10 µmol/L Semaglutide. The width of the wound was monitored by taking images at baseline (0 h) and after 48 h using a microscope (Thermofisher, USA). Analysis was performed using ImageJ software.

(6) Transwell migration and invasion assays

The transwell migration and invasion assays were conducted using a 24-well transwell chamber (Corning, USA) and 8-µm pore size membranes (Corning, USA). Cal27 or HSC4 cells were incubated with 0, 5, or 10 µmol/L Semaglutide for 48 h. For the migration assays, Cal27 (4×10^5) or HSC4 (1×10^5) cells in 200µL of serum-free culture medium were inserted into the upper chamber, while the lower chamber was supplemented with 600 µL of medium supplemented with 20% FBS and incubated for 24 h. The invasion assays followed the same procedure as the migration assays, but the cells were placed on a Matrigel-coated membrane (Corning, USA). Afterward, cells were fixed using 4% PFA for 15 min and then stained with 0.1% crystal violet for 30 min. Images were captured using an inverted microscope (Zeiss, Germany).

(7) Cell apoptosis assays

Cal27 or HSC4 cells (2×10^5) were seeded in 6-well plates and cultured with 0, 5, or 10 µmol/L Semaglutide for 48 h. Then cells and the supernatant were collected and washed twice with PBS, and re-suspended in 1×binding buffer. Subsequently, apoptosis was assessed using an Annexin V-FITC Apoptosis Detection Kit (Dojindo, Japan) according to the manufacturer's instructions. Briefly, 100 µL of the cell suspension was incubated with 5 µL of Annexin V-FITC and 5 µL of PI in the dark at RT for 15 min. The apoptotic cells were analyzed via flow cytometry using a flow cytometer (BD LSRFortessa, BD Biosciences, USA). A minimum of 10,000 events were acquired for each sample, and the data were analyzed using FlowJo software.

Quantitative real-time PCR (qRT-PCR)

Cal27 or HSC4 cells (2×10^5) were seeded in 6-well plates and incubated with 0, 5, or 10 µmol/L Semaglutide for 48 h. Then total RNA was extracted from the cells using a cell RNA rapid extraction kit (Gooniebio, China). Then, 1 µg of total RNA was reverse transcribed via the HiScript III All-in-one RT SuperMix Perfect for qPCR Kit (Vazyme, China), and SYBR Green-based qRT – PCR was performed using the Universal SYBR qPCR Master Mix Kit (Vazyme, China) on a QuantStudio 5 Real-Time PCR System (Thermofisher, USA) according to the manufacturer's instructions. The primer sequences for qRT-PCR are shown in Table 1.

Table 1 Detailed information of the primer sequences for qRT-PCR

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
GLP-1R	CCTCCTGCCACAGACTTGTT	GCTGACATTCACGAACGAGC
GAPDH	GTCGGAGTCAACGGATTTGG	AGTTGAGGTCAATGAAGGGGTC

Western blot analysis

Cal27 or HSC4 cells (2×10^5) were seeded in 6-well plates and cultured with 0, 5, or 10 μmol/L Semaglutide for 48 h. Total protein was then extracted from the cells using RIPA lysis buffer containing both protease inhibitors and phosphatase inhibitors (Cwbio, China). 20 μg of protein samples were separated by electrophoresis and subsequently transferred onto PVDF membranes (Millipore, USA). Thereafter, the membranes were blocked with a solution of 5% non-fat milk for 1 h at room temperature (RT) and then incubated with primary antibodies at 4℃ overnight. Subsequently, the membranes were incubated with corresponding secondary antibodies (1:5000, EMAR, China) for 1 h at RT. The target proteins were detected using Enhanced Chemiluminescence (ECL) reagent (Millipore, USA), alongside a chemiluminescence imaging system (Licor, USA). The primary antibodies utilized for western blot are detailed in Table 2.

Immunohistochemistry (IHC)

Tumor specimens from both human and mouse sources were sectioned into 4-μm thick slices, followed by dewaxing and hydration. The samples were then treated with 3% hydrogen peroxide at RT and subsequently antigen-retrieved in the citrate solution (pH 6.0) using a microwave oven for 10 min. After blocking with 1% FBS at RT for 30 min to prevent non-specific binding, specimens were incubated with the primary antibodies at 4 °C overnight. The next day, tissue sections were incubated with corresponding secondary antibodies (1:200, Servicebio, China) for 30 min at RT. A DAB detection kit (Gene Tech, China) was used for chromogenic detection, and hematoxylin (Servicebio, China) was used to counterstain the nucleus. After the staining procedures were completed, the tissue sections were washed in running water, dehydrated, made transparent, and sealed. Images of the prepared slides were taken via Aperio AT2 (Leica, Germany). Details regarding the primary antibodies utilized in IHC are provided in Table 3. H-score was used to evaluate the immunohistochemical staining results according to the following formula: H-score = Σ (Pi × i), where Pi denotes the proportion of positively stained cells at a specific intensity level, and i represents the staining intensity, which is usually scored as 0, 1, 2, or 3.

Table 2 Detailed information of primary antibodies used in western blot

Primary antibodies	Company	Cat.No	Dilution
GLP-1R	Novus, USA	NBP1-97308	1:1000
Ki67	Affinity, China	AF0198	1:1000
PCNA	Servicebio, China	GB11010-1–100	1:1000
E-cadherin	Proteintech, China	20874–1-AP	1:20000
Vimentin	Proteintech, China	10366–1-AP	1:10000
Bcl-xL	CST, USA	2764S	1:1000
Bax	CST, USA	2772 T	1:1000
p-P38	CST, USA	8690S	1:1000
P38	CST, USA	4511S	1:1000
p-SAPK/JNK	CST, USA	4668S	1:1000
SAPK/JNK	CST, USA	9252S	1:1000
p-Erk1/2	CST, USA	4370S	1:2000
Erk1/2	CST, USA	4695S	1:1000
β-Tubulin	Proteintech, China	10094-1-AP	1:10000

Animals and tumor implantation experiments

All animal studies were approved by the Laboratory Animals Ethics Committee of Sun Yat-sen University (SYSU-IACUC-2024–001114). A total of 18 male BALB/c nude mice (nu/nu, aged 4–6 weeks) were purchased from Gempharmatech (China) and allowed to acclimate for one week. To establish nude mouse xenograft tumor models, approximately 5×10^6 Cal27 cells per site were subcutaneously injected into the armpits of mice. Five days after the tumor cells were injected, the mice were randomly divided into three groups: a normal control group (without manipulation), an NS group (mice received injections of 100μL normal saline under the skin three times per week for three weeks), and a Semaglutide group (mice received injections of 100μL Semaglutide solution at a dosage of 3 μmol/kg under the skin three times per week for three weeks). The dosage of Semaglutide was determined based on preliminary experiments and Semaglutide is diluted with normal saline (NS). The body weight and tumor volume of the mice were recorded three times per week for three weeks. All mice were sacrificed on day 21, after which the tumors, along with the liver, lung, and kidney tissues of the mice were removed and fixed for further experiments.

Table 3 Detailed information of primary antibodies used in IHC assays

Primary antibodies	Company	Cat. No	Dilution
GLP-1R	Novus, USA	NBP1-97308	1:500
Ki67	CST, USA	12202S	1:100
PCNA	Servicebio, China	GB11010-1–100	1:1000
E-cadherin	Proteintech, China	20874–1-AP	1:10000
Vimentin	Proteintech, China	10366–1-AP	1:1000
Bcl-xL	CST, USA	2764S	1:2000
Bax	CST, USA	2772 T	1:1000
p-P38	CST, USA	8690S	1:50
P38	CST, USA	4511S	1:100

Statistical analysis

The normality of the data was tested using the Shapiro–Wilk test. Differences between two groups were estimated by the student's t-test, while comparisons among three or more groups were performed with one-way ANOVA followed by Tukey multiple comparison test. Two-way ANOVA with Tukey's multiple comparisons was used to assess the statistical differences between groups in time-dependent proliferation assays conducted on the IncuCyte S3 platform. All in vitro experiments were repeated at least three times, and IHC staining for xenograft tumors included 6 samples per group. Data are expressed as means ± standard deviation (SD), and differences were considered significant for values of $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics and GraphPad Prism.

Results

The expression of GLP-1R was heightened in OSCC compared to normal levels

To detect the expression of GLP-1R in OSCC, we extracted RNA and proteins from CFPAC-1 cells (human pancreatic cancer cells, as a positive control), NOK cells (human normal squamous epithelial cells, normal oral keratinocytes) and seven OSCC cell lines for qRT-PCR and western blot analysis. Our findings indicated that GLP-1R was expressed in OSCC cells at levels higher than those observed in NOK cells. We collected both OSCC tissues and normal tissues for IHC staining, which revealed that GLP-1R was expressed in human OSCC tissues with elevated levels compared to normal tissues. Then we extracted proteins from Cal27 and HSC4 cells with 0, 5, or 10 μmol/L Semaglutide treatment for 48 h for western blot. The results showed that Semaglutide treatment increased GLP-1R expression of Cal27 and HSC4 cells, suggesting that Semaglutide may act on GLP-1R in OSCC cells to exert further effects (Fig. 1).

Semaglutide inhibited the proliferation of OSCC cells

To investigate the effects of Semaglutide on the proliferation of OSCC cells, we employed CCK8 assays to determine the cell viability, utilized the IncuCyte S3 platform for continuous monitoring of the cell confluence, and performed colony formation assays to evaluate cellular clonogenic ability. Our results demonstrated that Semaglutide exhibited a dose-dependent anticancer activity in two OSCC cell lines, Cal27 and HSC4 cells. The expression levels of proteins related to cell proliferation were detected by western blot. We observed that Semaglutide significantly reduced the expressions of Ki67 and PCNA. Overall, our findings indicated that Semaglutide inhibited the proliferation of OSCC cells (Fig. 2).

Semaglutide inhibited the migration and invasion of OSCC cells

We conducted scratch assays, transwell migration and invasion assays to investigate the impact of Semaglutide on the invasion and migration abilities of OSCC cells. The results showed that as the concentration of Semaglutide increased, the scratch area expanded while the number of cells traversing the chambers decreased. Then we detected the expression of epithelial-mesenchymal transition (EMT)-related proteins (E-cadherin and Vimentin) by western blot and found that Semaglutide increased the expression of E-cadherin and decreased the expression of Vimentin. Collectively, these results revealed that Semaglutide suppressed migration, invasion, and EMT in OSCC cells (Fig. 3).

Semaglutide promoted the apoptosis of OSCC cells

Annexin V-FITC/PI staining was used to explore the effect of Semaglutide on the apoptosis level of OSCC cells by flow cytometry. The results disclosed that the proportions of early and late apoptotic cells were significantly elevated compared to control groups, which indicated that Semaglutide treatment enhanced the apoptosis rates of Cal27 and HSC4 cells in a dose-dependent manner. Subsequently, the expressions of cell apoptosis related proteins were detected by western blot. We discovered that Semaglutide decreased the expression of Bcl-xL, an anti-apoptotic protein, while concurrently increasing the expression of Bax, a pro-apoptotic protein. In summary, our results demonstrated that Semaglutide promoted apoptosis of OSCC cells (Fig. 4).

Inhibitory effect of Semaglutide on the growth and development of OSCC in vivo

We established a xenograft transplantation model of OSCC to investigate the anti-OSCC effect of Semaglutide in vivo. The results obtained from animal experiments were consistent with those derived from in vitro studies. Semaglutide manifested an inhibitory effect on OSCC growth in vivo, without causing any significant changes to the body weight of mice. After 3 weeks of treatment, we excised the tumors from the mice. The data showed that both the tumor volume and tumor weight in the Semaglutide group were smaller than those in the control and NS groups. Subsequently, IHC was utilized to detect the expression levels of Ki67, PCNA, E-cadherin, Vimentin, Bcl-xL, Bax, and GLP-1R in tumor tissues. As the results revealed, Semaglutide increased the expression of E-cadherin, Bax, and GLP-1R, while

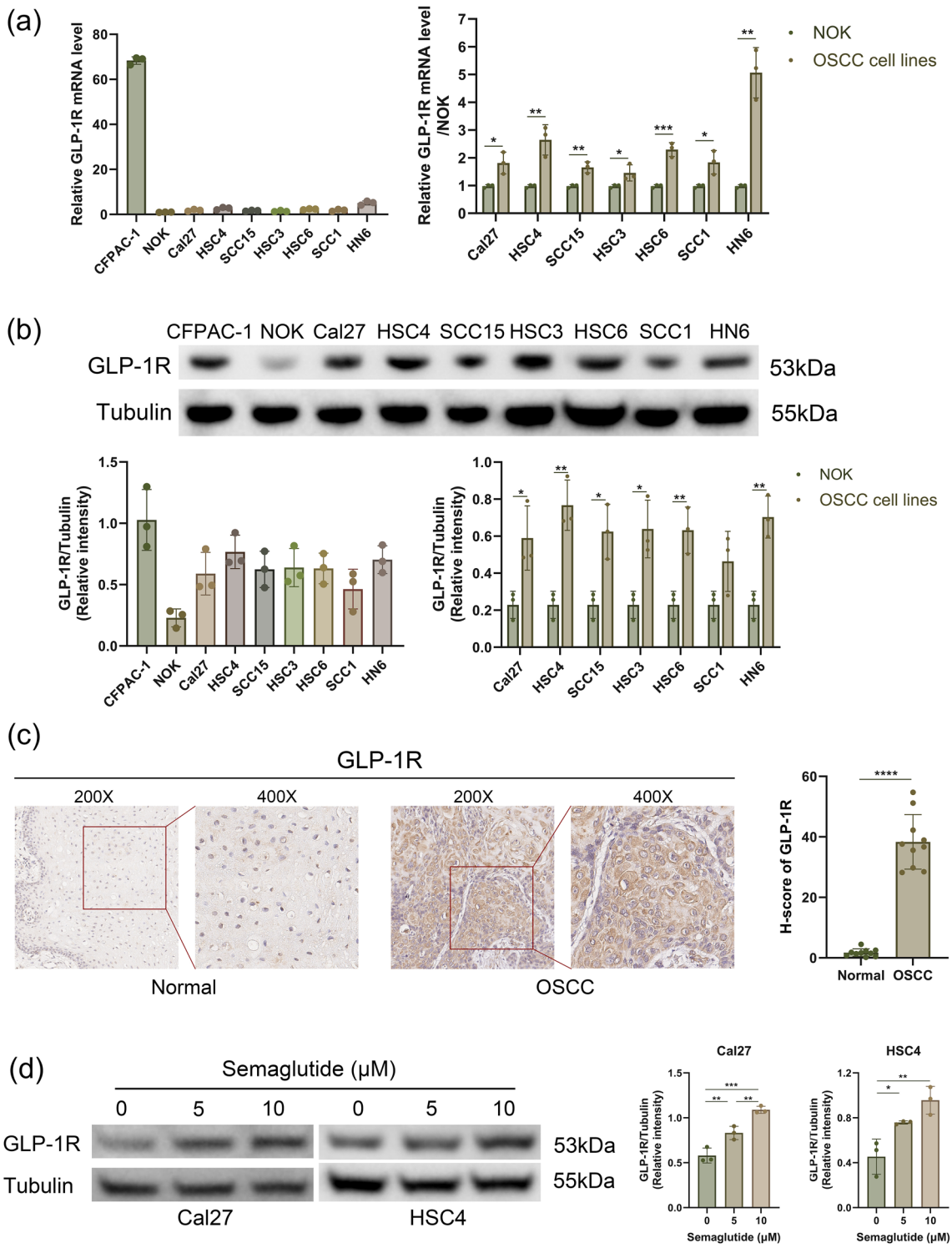


Fig. 1 The expression of GLP-1R was elevated in OSCC compared to normal levels. **a**, **b** The gene and protein expression levels of GLP-1R, detected by qRT-PCR and western blot assays, were higher in OSCC cells than those observed in NOK cells. **c** Representative images of GLP-1R expression in OSCC and normal tissues by IHC staining (n = 10). The results showed that GLP-1R was expressed in human OSCC tissues with elevated levels compared to normal tissues. **d** After treatment with Semaglutide (0, 5, or 10 μmol/L) for 48 h, the protein levels of GLP-1R in Cal27 and HSC4 cells were increased, as detected by western blot. (N = 3; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; student's t test or one-way ANOVA with Tukey's multiple comparisons)

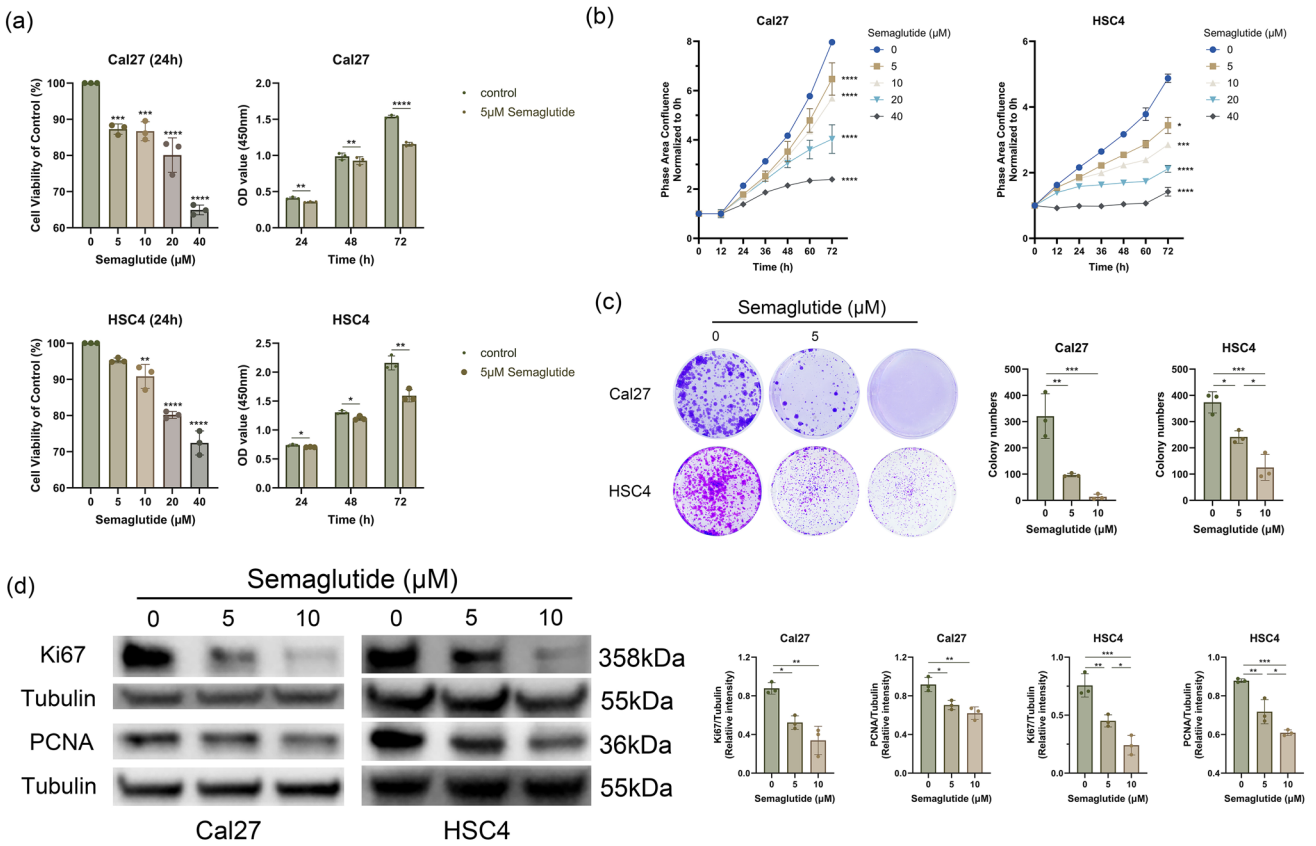


Fig. 2 Semaglutide inhibited the proliferation of OSCC cells. **a**, **b** With treatment with Semaglutide at concentrations of 0, 5, 10, 20, or 40 μmol/L, the cell viability of Cal27 and HSC4 cells was assessed using CCK-8 assays and the cell confluence was continuously monitored by the IncuCyte S3 System. The results showed that Semaglutide exhibited a dose-dependent and time-dependent anticancer activity in Cal27 and HSC4 cells. (* control vs. treatment) **c** Representative images of clonal formation assays of Cal27 and HSC4 cells treated with 0, 5, or 10 μmol/L Semaglutide. The results showed that Semaglutide inhibited the proliferation of Cal27 and HSC4 cells. **d** After treatment with Semaglutide at concentrations of 0, 5, or 10 μmol/L for 48 h, the protein levels of Ki67 and PCNA in Cal27 and HSC4 cells were decreased, as measured by western blot. (N = 3; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; student's t test, one-way or two-way ANOVA with Tukey's multiple comparisons)

decreasing the expression of Ki67, PCNA, Vimentin, and Bcl-xL, which were consistent with in vitro experiments. Generally, our study demonstrated that Semaglutide inhibited OSCC growth in vivo (Fig. 5).

Semaglutide activated the P38 MAPK signaling pathway

To further explore the mechanism by which Semaglutide inhibits the progression of OSCC, we investigated the phosphorylation status of three MAPK signaling pathways (ERK1/2, SAPK/JNK and P38) in Cal27 and HSC4 cells after Semaglutide treatment (0, 5, or 10 μmol/L, 48 h) by western blot analysis. The results revealed that Semaglutide selectively increased the phosphorylation levels of P38 (p-P38) in a dose-dependent manner, while no significant changes were observed in the phosphorylation status of ERK1/2 or SAPK/JNK and total protein levels of MAPKs, indicating that Semaglutide specifically modulates P38 activation rather than broadly altering MAPK pathway components. To further assess the functional role of P38 activation in Semaglutide's anti-tumor effects, Cal27 and HSC4 cells were pretreated with BIRB796 (10 μmol/L, the p38 inhibitor) for 2 h, followed by treatment with Semaglutide (5 μmol/L) for 48 h. The results of western blot showed that co-treatment increased Bcl-xL expression and decreased Bax expression, suggesting that BIRB796 significantly attenuated Semaglutide's effect on apoptosis-related proteins. These results indicated that the apoptosis induced by Semaglutide was related to the activation of P38 pathway. Consistent with in vitro findings, IHC staining of OSCC xenograft tumors showed an increase of p-P38 levels in Semaglutide-treated groups compared to controls, while total P38 expression remained unchanged. In conclusion, Semaglutide specifically modulated P38 activation, which was related to its pro-apoptosis effect on OSCC (Fig. 6).

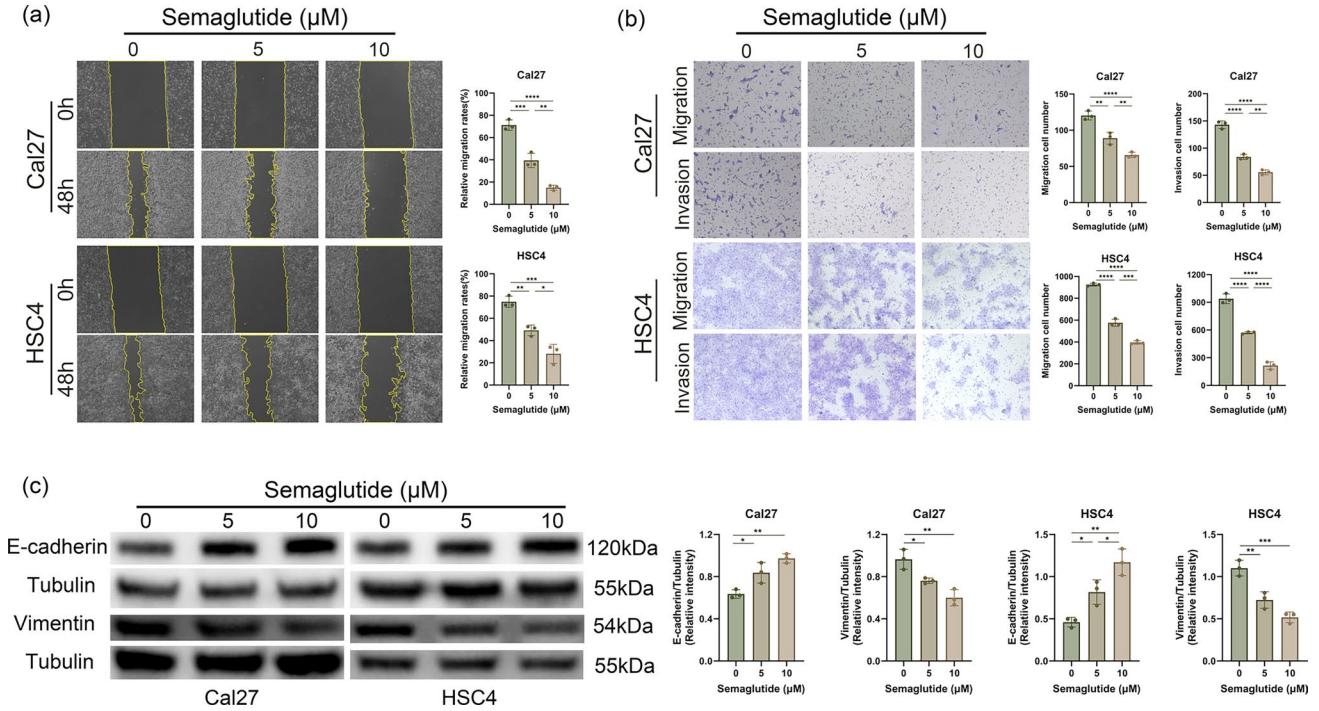


Fig. 3 Semaglutide Inhibited the migration and invasion of OSCC cells. **a** The migration ability of Cal27 and HSC4 cells with Semaglutide (0, 5, or 10 μmol/L) treatment was determined by wound healing assays. As the concentration of Semaglutide increased, the scratch area expanded, indicating that the cell migration ability was inhibited by Semaglutide. **b** After treatment with Semaglutide at concentrations of 0, 5, or 10 μmol/L for 48 h, the migration and invasion abilities of Cal27 and HSC4 cells were measured by Transwell assays. The results showed that Semaglutide treatment decreased the number of cells traversing the chambers, suggesting that it suppressed both migration and invasion. **c** After Semaglutide (0, 5, or 10 μmol/L) treatment for 48 h, the protein levels of E-cadherin and Vimentin of Cal27 and HSC4 cells were evaluated by western blot. The results showed that Semaglutide increased the expression of E-cadherin and decreased the expression of Vimentin. (N = 3; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; one-way ANOVA with Tukey's multiple comparisons)

Discussion

OSCC and DM represent two major global health challenges, with rising incidence rates worldwide. (Ahmad et al. 2022; Li et al. 2024a, b). Substantial improvements in both glycaemic control and body weight, along with established cardiovascular benefits, have positioned GLP-1RAs as the first-line injectable therapy for DM (Heise 2022). Semaglutide, a long-acting GLP-1RA, has been approved for the treatment of T2DM and obesity by the Food and Drug Administration (FDA) (Ala and Moheb 2024). With the application of GLP-1RAs, the correlation between GLP1-RAs and tumors has attracted considerable attention in recent years (Ji et al. 2024). However, previous studies primarily focus on short-activating GLP-1RAs with controversial results, while studies on long-acting GLP-1RAs such as Semaglutide are very limited (Pu et al. 2023).

In order to explore the potential effect of Semaglutide on OSCC, we first determined the expression of GLP-1R in OSCC. Our findings revealed significantly elevated GLP-1R expression levels in both OSCC tissues and cell lines compared to normal controls. Furthermore, Semaglutide treatment induced a dose-dependent upregulation of GLP-1R expression in OSCC cells, suggesting a potential positive feedback mechanism. Our findings are in line with those from previous studies. Liu's study found that GLP-1R was widely expressed in many breast cancer cell lines, and the mRNA and protein expression levels of GLP-1R were increased in MDA-MB-231 cells treated with GLP-1RA Liraglutide(Liu et al. 2022). Similar results have been reported in studies of endometrial and pancreatic cancers(Zhao et al. 2014; Kanda et al. 2018). The correlation between GLP-1R expression and OSCC patient outcomes should be explored further because of the differences in the expression of GLP-1R in OSCC and normal tissues. Recent study demonstrated differential prognostic implications of GLP-1R expression across cancer types(Ungvari et al. 2025). The results turned out that increased GLP-1R expression correlated with improved overall survival in cancers such as breast cancer, bladder cancer, and esophageal adenocarcinoma, while predicted survival outcomes in cancers such as cervical squamous cell carcinoma, lung squamous cell carcinoma. In addition, no significant association was observed in head and neck squamous cell carcinoma

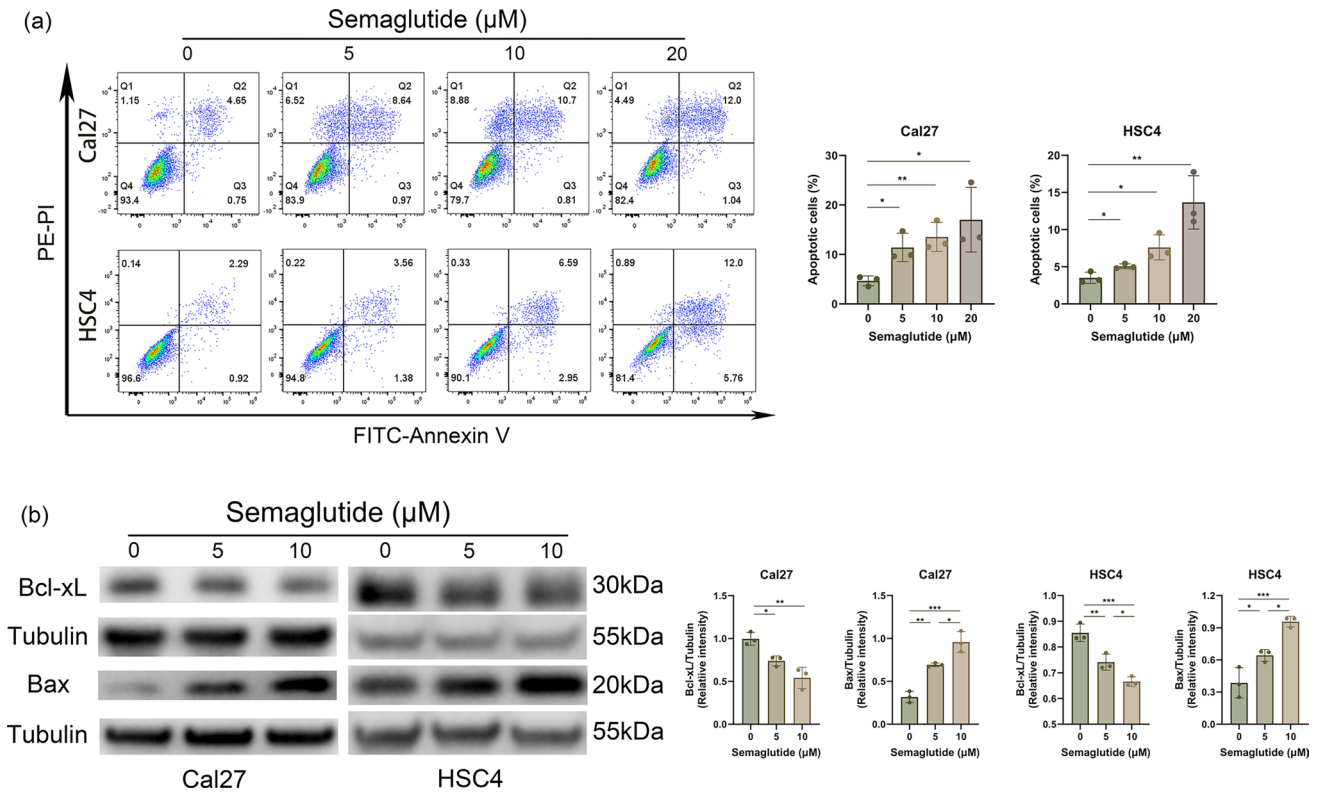
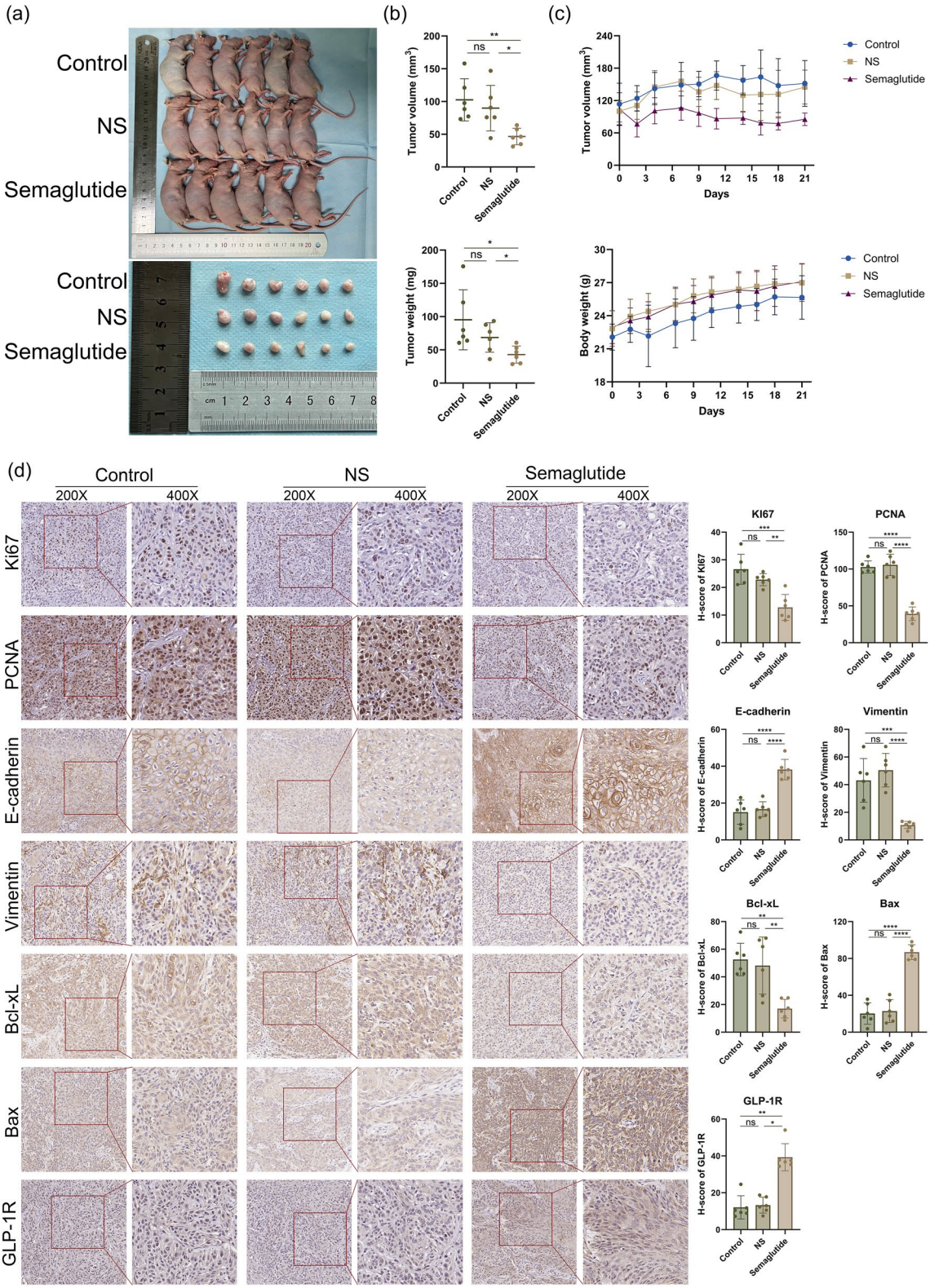


Fig. 4 Semaglutide promoted the apoptosis of OSCC cells. **a** After treatment with Semaglutide at concentrations of 0, 5, or 10 μmol/L for 48 h, the apoptosis effects of Cal27 and HSC4 cells were measured by flow cytometry assays with AnnexinV FITC/PI dual staining. The results indicated that Semaglutide treatment enhanced the apoptosis rates of Cal27 and HSC4 cells in a dose-dependent manner. **b** The protein levels of Bcl-xL and Bax of Cal27 and HSC4 cells after Semaglutide treatment (0, 5, or 10 μmol/L, 48 h) were measured by western blot. Semaglutide decreased the expression of Bcl-xL while concurrently increasing the expression of Bax. (N = 3; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; student's t test or one-way ANOVA with Tukey's multiple comparisons)

(HNSC), esophageal squamous cell carcinoma, or colon cancer. Notably, HNSC includes tumors from the oral cavity, pharynx, and larynx, which may exhibit distinct molecular profiles and clinical behaviors (Johnson et al. 2020). Therefore, survival trends observed in HNSCC cohorts may not precisely mirror OSCC-specific outcomes, and further research is necessary.

Tumor proliferation and metastasis are the primary factors contributing to cancer progression. Our results showed that Semaglutide inhibited the proliferation, migration, invasion and promoted the apoptosis of OSCC cell lines. In addition, Semaglutide treatment inhibited epithelial-mesenchymal transition (EMT) in OSCC cell lines, which is a crucial process involved in embryonic development and tissue regeneration (Huang et al. 2022). In the context of cancer, EMT can facilitate migration and invasion while regulating tumor stemness; it also plays a role in tumor initiation and malignant transformation as well as increasing resistance to chemotherapy and immunotherapy (Brabletz et al. 2021). Moreover, the inhibitory effect of Semaglutide on OSCC was further validated in the tumor xenograft model in vivo. Our results are consistent with studies of GLP-1RAs in other malignancies. A recent study reported that Semaglutide inhibited the growth and progression of breast cancer by enhancing the acquired antitumor immunity (Stanisavljevic et al. 2024). Besides, related studies have found that GLP-1RAs could limit the growth of pancreatic cancer, prostate cancer and colorectal cancer by inhibiting the PI3K/Akt/mTOR signal pathway (Zhao et al. 2014; Wenjing et al. 2020; Tong et al. 2022). Similarly, GLP-1RAs were also demonstrated to inhibited cholangiocarcinoma, breast and cervical cancer, implying the potential application of GLP-1RAs for the treatment of these tumors (Zhao et al. 2021; Trakoonsenathong et al. 2024). However, GLP-1RAs showed the opposite effect in some tumors. Research found that GLP-1RA promoted the proliferation of neuroendocrine neoplasm cells, and boosted survival, migration and invasion of endometrial cancer cells (Li et al. 2024a, b; Shilyansky et al. 2025). These findings indicate that the role of GLP-1RAs varies across different types of tumors, necessitating further investigation.

Mitogen-activated protein kinases (MAPKs), including ERK1/2, P38, and JNK/SAPK, are pivotal in regulating signaling cascades that translate extracellular stimuli into



essential biological responses such as cell survival, proliferation, differentiation, metabolism, motility, and apoptosis (Li et al. 2020). Previous studies have proposed that phosphorylation of ERK1/2 promoted cell migration, proliferation, and metastasis in OSCC (Chang et al. 2021; Yang et al. 2024). However, the role of P38 and SAPK / JNK in OSCC is controversial. Some studies have proposed that the activation of P38 and SAPK/JNK contributes to the malignant growth

◂**Fig. 5** Inhibitory effect of Semaglutide on growth and development of OSCC in vivo. **a** Representative images of tumors in mice and excised tumors from groups receiving no treatment, treated with NS, or Semaglutide. **b** The volume and weight of the tumor removed in the Semaglutide group were smaller than those in the control and NS groups. **c** The subcutaneous tumor volume and body weight in each group were assessed three times a week for each group. The data showed that Semaglutide inhibited the growth of OSCC in vivo, without any significant effect on the body weight of mice. **d** Representative images of Ki67, PCNA, E-cadherin, Vimentin, Bcl-xL, Bax, and GLP-1R expression in tumor tissues by IHC staining. The results revealed that Semaglutide increased the expression of E-cadherin, Bax, and GLP-1R, while decreasing the expression of Ki67, PCNA, Vimentin, and Bcl-xL. (N = 6; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; one-way ANOVA with Tukey's multiple comparisons)

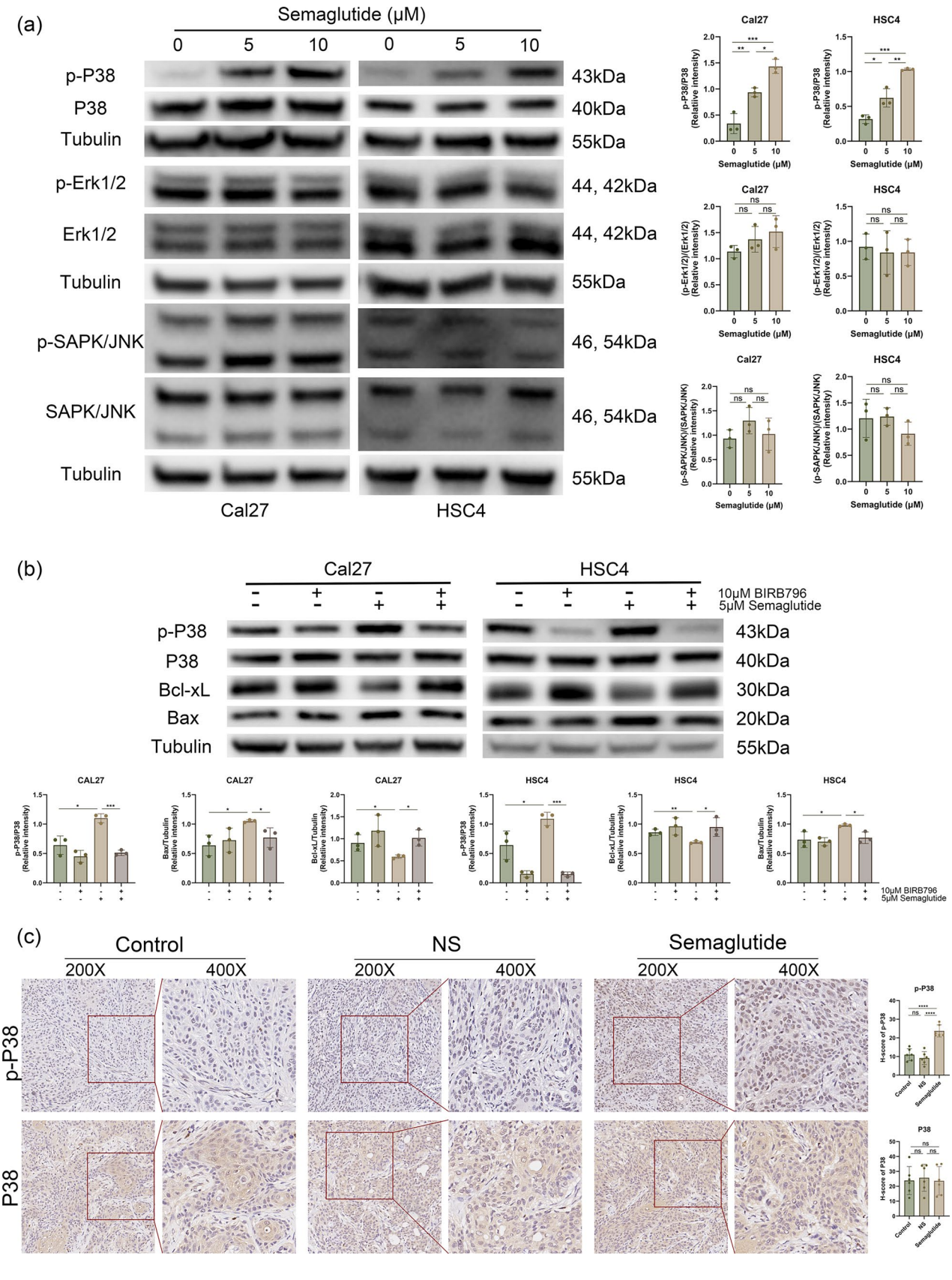
of OSCC, while other research has indicated that they may function as tumor suppressor genes (Mishima et al. 2002; Chen et al. 2017; Li et al. 2020; Huang et al. 2024). In our study, Semaglutide treatment promoted an increase in phosphorylated P38 without significant effect on the activation of ERK1/2 and JNK/SAPK signaling pathways. P38 pathway is activated by various actors (environmental stimuli, inflammatory cytokines, etc.), which leads to the phosphorylation of numerous transcriptional regulators that coordinate particular gene expression programs and then modulating various cellular functions (Yong et al. 2009; Martinez-Limon et al. 2020). Most studies suggest that P38 is related to apoptosis, which can affect death receptors, survival pathways, or pro-and antiapoptotic Bcl-2 family proteins (Cargnello and Roux 2011). We foung that the P38 inhibitor BIRP796 attenuated the role of Semaglutide in promoting OSCC apoptosis, suggesting that the apoptosis induced by Semaglutide was related to the activation of P38 pathway. Previous studies have shown that GLP-1 activated the P38 signaling pathway in breast cancer cells, and P38 inhibitors abolished the anti-breast cancer effects of exendin-4 (Ligumsky et al. 2012), which are consistent with our results.

Due to the increasing prevalence of OSCC and DM, along with a notable correlation between the two, it is imperative to scrutinize the safety profile of anti-diabetic medications. Our study is pioneering in demonstrating that GLP-1RA Semaglutide exerts an inhibitory effect on OSCC, suggesting that the use of GLP-1RAs might not heighten the risk of OSCC but could potentially confer protective effects. Furthermore, Semaglutide may be a novel potential agent in the investigation of new therapeutic strategies and the combination with current chemotherapy agents for OSCC.

Nonetheless, this study still harbors several limitations that need to be addressed in future studies. Firstly, functional studies using GLP-1R knockdown models should be conducted in the future to further verify whether the effects of Semaglutide are mediated entirely by GLP-1R. Secondly, it's necessary to expand the sample size to verify the universality of the conclusion about the difference of the GLP-1R expression in OSCC and normal tissues, focus on the clinical and pathological correlation between GLP-1R expression and OSCC, and further explore the relationship between GLP-1R and OSCC patient prognosis in the follow-up studies. What's more, while our subcutaneous xenograft model demonstrated significant tumor growth inhibition by Semaglutide, it does not fully recapitulate the tumor microenvironment (TME) or metastatic behavior of OSCC. Orthotopic models may provide more clinically relevant insights into the effects of Semaglutide on local invasion, lymphatic dissemination, and distant metastasis of OSCC. Finally, clinical validation is essential to confirm therapeutic potential and long-term safety. Future work should explore the risks and benefits of Semaglutide in patients with OSCC and the combination of Semaglutide with existing OSCC treatments, such as chemotherapy or immunotherapy.

Conclusion

In summary, our study first demonstrated that GLP-1R was expressed at significantly higher levels in OSCC tissues and cells compared with normal controls. Moreover, our research revealed that Semaglutide inhibited the proliferation, migration and invasion of OSCC cells and induced apoptosis in vitro. And it significantly attenuated the growth of xenograft OSCC growth in vivo. Furthermore, the apoptosis induced by Semaglutide was related to the activation of P38 MAPK signaling pathway. This study expanded our comprehension of the relationship between GLP-1RAs and OSCC and provided some supporting evidence for the safety of Semaglutide in clinical application.


(a)
Semaglutide (μM)
0 5 10 0 5 10
p-P38
P38
Tubulin
p-Erk1/2
Erk1/2
Tubulin
p-SAPK/JNK
SAPK/JNK
Tubulin
43kDa
40kDa
55kDa
44, 42kDa
44, 42kDa
55kDa
46, 54kDa
46, 54kDa
55kDa
Cal27
HSC4
Cal27
HSC4
p-P38/P38 (Relative intensity)
(p-Erk1/2)/(Erk1/2) (Relative intensity)
(p-SAPK/JNK)/(SAPK/JNK) (Relative intensity)
Semaglutide (μM)
ns
(b)
Cal27
HSC4
10μM BIRB796
5μM Semaglutide
p-P38
P38
Bcl-xL
Bax
Tubulin
43kDa
40kDa
30kDa
20kDa
55kDa
CAL27
HSC4
p-P38/P38 (Relative intensity)
Bax/Tubulin (Relative intensity)
Bcl-xL/Tubulin (Relative intensity)
10μM BIRB796
5μM Semaglutide
(c)
Control
NS
Semaglutide
200X
400X
p-P38
P38
H-score of p-P38
H-score of P38
Control
NS
Semaglutide

◂**Fig. 6** Semaglutide activated the P38 MAPK signaling pathway. **a** Protein levels of MAPK signaling pathways of Cal27 and HSC4 cells after Semaglutide treatment (0, 5, or 10 μmol/L, 48 h) were measured by western blot. The results showed that Semaglutide increased the expression of p-P38 without influence on other marker proteins of MAPK signaling pathway. **b** After Semaglutide (5 μmol/L) and/or BIRB796 (10 μmol/L) treatment for 48 h, protein levels of p-P38, P38, Bcl-xL, and Bax of Cal27 and HSC4 cells were examined by western blot. The data revealed that co-treatment with BIRB796 and Semaglutide increased Bcl-xL expression and decreased Bax expression compared to treatment with Semaglutide alone. **c** Representative images of p-P38 and P38 in xenograft transplantation model of OSCC by IHC staining. The results showed that Semaglutide increased the expression of p-P38 without influence on total P38. (N = 3 for Fig. **a**, **b**, n = 6 for Fig. **c**; Mean ± SD; *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001; student's t test or one-way ANOVA with Tukey's multiple comparisons)

Acknowledgements The present study was supported by the Science and Technology Program of Guangzhou (Grant Number: 202206080009).

Author contributions C. W. wrote the main manuscript text and conducted methodology, investigation, and formal analysis. Z. W. and J. Z. contributed to validation and investigation. B. C. and Y. H. reviewed and edited the manuscript, supervised the study, curated data, and contributed to conceptualization and funding acquisition. All authors reviewed the manuscript.

Funding The present study was supported by the Science and Technology Program of Guangzhou (Grant Number: 202206080009).

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interests The authors declare no conflict of interests.

References

Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ (2022) Type 2 diabetes. Lancet 400:1803–1820. https://doi.org/10.1016/S0140-6736(22)01655-5

Ala M, Moheb AM (2024) The blood pressure-lowering property of subcutaneous semaglutide: a systematic review, meta-analysis, and meta-regression. J Endocrinol Invest. https://doi.org/10.1007/s40618-024-02459-3

Andreadis P, Karagiannis T, Malandris K, Avgerinos I, Liakos A, Manolopoulos A, Bekiari E, Matthews DR, Tsapas A (2018) Semaglutide for type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 20:2255–2263. https://doi.org/10.1111/dom.13361

Azoulay L, Filion KB, Platt RW, Dahl M, Dormuth CR, Clemens KK, Durand M, Juurlink DN, Targownik LE, Turin TC, Paterson JM, Ernst P (2016) Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ 352:i581. https://doi.org/10.1136/bmj.i581

Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP (2021) Dynamic EMT: a multi-tool for tumor progression. Embo J. https://doi.org/10.15252/embj.2021108647

Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Verges B, Marre M (2020) Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab 46:100–109. https://doi.org/10.1016/j.diabet.2019.101117

Cargnello M, Roux PP (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev 75:50–83. https://doi.org/10.1128/MMBR.00031-10

Chang WS, Tsai CW, Yang JS, Hsu YM, Shih LC, Chiu HY, Bau DT, Tsai FJ (2021) Resveratrol inhibited the metastatic behaviors of cisplatin-resistant human oral cancer cells via phosphorylation of ERK/p-38 and suppression of MMP-2/9. J Food Biochem 45:e13666. https://doi.org/10.1111/jfbc.13666

Chao AM, Tronieri JS, Amaro A, Wadden TA (2023) Semaglutide for the treatment of obesity. Trends Cardiovasc Med 33:159–166. https://doi.org/10.1016/j.tcm.2021.12.008

Chen BD, Zhao WC, Jia QA, Zhou WY, Bu Y, Wang ZZ, Wang F, Wu WJ, Wang Q (2013) Effect of the GLP-1 analog exendin-4 and oxaliplatin on intrahepatic cholangiocarcinoma cell line and mouse model. Int J Mol Sci 14:24293–24304. https://doi.org/10.3390/ijms141224293

Chen JC, Hsieh MC, Lin SH, Lin CC, Hsi YT, Lo YS, Chuang YC, Hsieh MJ, Chen MK (2017) Coronarin D induces reactive oxygen species-mediated cell death in human nasopharyngeal cancer cells through inhibition of p38 MAPK and activation of JNK. Oncotarget. https://doi.org/10.18632/oncotarget.22444

Dhillon S (2018) Semaglutide: first global approval. Drugs 78:275–284. https://doi.org/10.1007/s40265-018-0871-0

Dhillon AS, Hagan S, Rath O, Kolch W (2007) MAP kinase signalling pathways in cancer. Oncogene 26:3279–3290. https://doi.org/10.1038/sj.onc.1210421

Eftekhari S, Montazeri H, Tarighi P (2020) Synergistic anti-tumor effects of Liraglutide, a glucagon-like peptide-1 receptor agonist, along with Docetaxel on LNCaP prostate cancer cell line. Eur J Pharmacol 878:173102. https://doi.org/10.1016/j.ejphar.2020.173102

ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA, On BOTA (2023) 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. Diabetes Care 46:S140–S157. https://doi.org/10.2337/dc23-S009

Heise T (2022) Novel drugs for diabetes therapy. Handb Exp Pharmacol 274:415–438. https://doi.org/10.1007/164_2021_574

Holst JJ, Gromada J (2004) Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. Am

J Physiol Endocrinol Metab 287:E199–E206. https://doi.org/10.1152/ajpendo.00545.2003

Hu X, Wu J, Xiong H, Zeng L, Wang Z, Wang C, Huang D, Zhang T, Peng Y, Chen W, Xia K, Su T (2022) Type 2 diabetes mellitus promotes the proliferation, metastasis, and suppresses the apoptosis in oral squamous cell carcinoma. J Oral Pathol Med 51:483–492. https://doi.org/10.1111/jop.13244

Hu EH, Tsai ML, Lin Y, Chou TS, Chen TH (2024) A review and meta-analysis of the safety and efficacy of using glucagon-like peptide-1 receptor agonists. Medicina (Kaunas). https://doi.org/10.3390/medicina60030357

Huang Y, Hong W, Wei X (2022) The molecular mechanisms and therapeutic strategies of EMT in tumor progression and metastasis. J Hematol Oncol 15:129. https://doi.org/10.1186/s13045-022-01347-8

Huang S, Zhang J, Qiao Y, Pathak JL, Zou R, Piao Z, Xie S, Liang J, Ouyang K (2024) CHRDL1 inhibits OSCC metastasis via MAPK signaling-mediated inhibition of MED29. Mol Med 30:187. https://doi.org/10.1186/s10020-024-00956-y

Ibrahim SS, Ibrahim RS, Arabi B, Brockmueller A, Shakibaei M, Busselberg D (2024) The effect of GLP-1R agonists on the medical triad of obesity, diabetes, and cancer. Cancer Metastasis Rev. https://doi.org/10.1007/s10555-024-10192-9

Iwaya C, Nomiyama T, Komatsu S, Kawanami T, Tsutsumi Y, Hamaguchi Y, Horikawa T, Yoshinaga Y, Yamashita S, Tanaka T, Terawaki Y, Tanabe M, Nabeshima K, Iwasaki A, Yanase T (2017) Exendin-4, a glucagonlike peptide-1 receptor agonist, attenuates breast cancer growth by inhibiting NF-kappaB activation. Endocrinology 158:4218–4232. https://doi.org/10.1210/en.2017-00461

Ji L, He X, Min X, Yang H, Wu W, Xu H, Chen J, Mei A (2024) Glucagon-like peptide-1 receptor agonists in neoplastic diseases. Front Endocrinol (Lausanne) 15:1465881. https://doi.org/10.3389/fendo.2024.1465881

Johnson DE, Burtness B, Leemans CR, Lui V, Bauman JE, Grandis JR (2020) Head and neck squamous cell carcinoma. Nat Rev Dis Primers 6:92. https://doi.org/10.1038/s41572-020-00224-3

Kanda R, Hiraike H, Wada-Hiraike O, Ichinose T, Nagasaka K, Sasajima Y, Ryo E, Fujii T, Osuga Y, Ayabe T (2018) Expression of the glucagon-like peptide-1 receptor and its role in regulating autophagy in endometrial cancer. BMC Cancer 18:657. https://doi.org/10.1186/s12885-018-4570-8

Koehler JA, Kain T, Drucker DJ (2011) Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Endocrinology 152:3362–3372. https://doi.org/10.1210/en.2011-1201

Li Z, Liu FY, Kirkwood KL (2020) The p38/MKP-1 signaling axis in oral cancer: impact of tumor-associated macrophages. Oral Oncol 103:104591. https://doi.org/10.1016/j.oraloncology.2020.104591

Li JH, Hsin PY, Hsiao YC, Chen BJ, Zhuang ZY, Lee CW, Lee WJ, Vo T, Tseng CF, Tseng SF, Lee IT (2024a) A narrative review: repurposing metformin as a potential therapeutic agent for oral cancer. Cancers (Basel). https://doi.org/10.3390/cancers16173017

Li W, Lyu W, Liu S, Ruan F, Zhang X (2024b) GLP1R boosts survival, migration and invasion of endometrial cancer cells and protects against ferroptotic cell death. J Obstet Gynaecol 44:2301324. https://doi.org/10.1080/01443615.2023.2301324

Ligumsky H, Wolf I, Israeli S, Haimsohn M, Ferber S, Karasik A, Kaufman B, Rubinek T (2012) The peptide-hormone glucagon-like peptide-1 activates cAMP and inhibits growth of breast cancer cells. Breast Cancer Res Treat 132:449–461. https://doi.org/10.1007/s10549-011-1585-0

Liu ZZ, Duan XX, Yuan MC, Yu J, Hu X, Han X, Lan L, Liu BW, Wang Y, Qin JF (2022) Glucagon-like peptide-1 receptor activation by liraglutide promotes breast cancer through NOX4/ROS/VEGF pathway. Life Sci 294:120370. https://doi.org/10.1016/j.lfs.2022.120370

Ma X, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, Chen Z, Luo S, Zheng X, Weng J, Xu S (2021) GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. Int J Biol Sci 17:2050–2068. https://doi.org/10.7150/ijbs.59965

Marassi M, Fadini GP (2025) Real-world evidence on oral semaglutide for the management of type 2 diabetes. a narrative review for clinical practice. Clin Ther 47:102–110. https://doi.org/10.1016/j.clinthera.2024.11.005

Martinez-Limon A, Joaquin M, Caballero M, Posas F, de Nadal E (2020) The p38 pathway: from biology to cancer therapy. Int J Mol Sci. https://doi.org/10.3390/ijms21061913

Mishima K, Inoue K, Hayashi Y (2002) Overexpression of extracellular-signal regulated kinases on oral squamous cell carcinoma. Oral Oncol 38:468–474. https://doi.org/10.1016/s1368-8375(01)00104-x

Nagendra L, Bg H, Sharma M, Dutta D (2023) Semaglutide and cancer: a systematic review and meta-analysis. Diabetes Metab Syndr 17:102834. https://doi.org/10.1016/j.dsx.2023.102834

Pandey S, Mangmool S, Parichatikanond W (2023) Multifaceted roles of GLP-1 and its analogs: a review on molecular mechanisms with a cardiotherapeutic perspective. Pharmaceuticals (Basel). https://doi.org/10.3390/ph16060836

Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi N, Spiazzi BF, Lopes JG, Colpani V, Gerchman F (2021) Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis. J Clin Endocrinol Metab 106:912–921. https://doi.org/10.1210/clinem/dgaa891

Pu Z, Yang Y, Qin S, Li X, Cui C, Chen W (2023) The effect of liraglutide on lung cancer and its potential protective effect on high glucose-induced lung senescence and oxidative damage. Front Biosci (Landmark Ed). https://doi.org/10.31083/j.fbl2810259

Ramos-Garcia P, Roca-Rodriguez M, Aguilar-Diosdado M, Gonzalez-Moles MA (2021) Diabetes mellitus and oral cancer/oral potentially malignant disorders: a systematic review and meta-analysis. Oral Dis 27:404–421. https://doi.org/10.1111/odi.13289

Sharma D, Verma S, Vaidya S, Kalia K, Tiwari V (2018) Recent updates on GLP-1 agonists: current advancements & challenges. Biomed Pharmacother 108:952–962. https://doi.org/10.1016/j.biopha.2018.08.088

Shilyansky JS, Chan CJ, Xiao S, Gribovskaja-Rupp I, Quelle DE, Howe JR, Dillon JS, Ear PH (2025) GLP-1R agonist promotes proliferation of neuroendocrine neoplasm cells expressing GLP-1 receptors. Surgery 179:108943. https://doi.org/10.1016/j.surg.2024.09.052

Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbol JD, Hansen T, Bain SC (2017) Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 5:251–260. https://doi.org/10.1016/S2213-8587(17)30013-X

Stanisavljevic I, Pavlovic S, Simovic MB, Jurisevic M, Krajnovic T, Mijatovic S, Spasojevic M, Mitrovic S, Corovic I, Jovanovic I (2024) Semaglutide decelerates the growth and progression of breast cancer by enhancing the acquired antitumor immunity. Biomed Pharmacother 181:117668. https://doi.org/10.1016/j.biopha.2024.117668

Suri S, Boora GS, Kaur R, Chauhan A, Ghoshal S, Pal A (2024) Recent advances in minimally invasive biomarkers of OSCC: from generalized to personalized approach. Front Oral Health 5:1426507. https://doi.org/10.3389/froh.2024.1426507

Tong G, Peng T, Chen Y, Sha L, Dai H, Xiang Y, Zou Z, He H, Wang S (2022) Effects of GLP-1 receptor agonists on biological behavior of colorectal cancer cells by regulating PI3K/AKT/mTOR signaling pathway. Front Pharmacol 13:901559. https://doi.org/10.3389/fphar.2022.901559

Trakoonsenathong R, Kunprom W, Aphivatanasiri C, Yueangchantuek P, Pimkeeree P, Sorin S, Khawkhiaw K, Chiu CF, Okada S, Wongkham S, Saengboonmee C (2024) Liraglutide exhibits potential anti-tumor effects on the progression of intrahepatic cholangiocarcinoma, in vitro and in vivo. Sci Rep 14:13726. https://doi.org/10.1038/s41598-024-64774-2

Ueda P, Wintzell V, Melbye M, Eliasson B, Svensson AM, Franzen S, Gudbjornsdottir S, Hveem K, Jonasson C, Svanstrom H, Pasternak B (2021) Use of incretin-based drugs and risk of cholangiocarcinoma: scandinavian cohort study. Diabetologia 64:2204–2214. https://doi.org/10.1007/s00125-021-05508-1

Ungvari Z, Bartha A, Ungvari A, Fekete M, Bianchini G, Gyorffy B (2025) Prognostic impact of glucagon-like peptide-1 receptor (GLP1R) expression on cancer survival and its implications for GLP-1R agonist therapy: an integrative analysis across multiple tumor types. Geroscience. https://doi.org/10.1007/s11357-024-01494-5

Vegh A, Banyai D, Ujpal M, Somogyi KS, Biczo Z, Kammerhofer G, Nemeth Z, Hermann P, Payer M, Vegh D (2022) Prevalence of diabetes and impaired fasting glycemia in patients with oral cancer: a retrospective study in hungary. Anticancer Res 42:109–113. https://doi.org/10.21873/anticanres.15464

Verma A, Goyal A (2024) Beyond insulin: the Intriguing role of GLP-1 in Parkinson's disease. Eur J Pharmacol 982:176936. https://doi.org/10.1016/j.ejphar.2024.176936

Wenjing H, Shao Y, Yu Y, Huang W, Feng G, Li J (2020) Exendin-4 enhances the sensitivity of prostate cancer to enzalutamide by targeting Akt activation. Prostate 80:367–375. https://doi.org/10.1002/pros.23951

Yang J, Ren Z, Wang F, Zheng J, Zhuang Z, Zeng Y (2024) gamma-Synuclein promotes proliferation and inhibits apoptosis of oral squamous cell carcinoma via JAK2/STAT5b signaling pathway. Am J Cancer Res 14:2408–2423. https://doi.org/10.62347/FLIM3367

Yong HY, Koh MS, Moon A (2009) The p38 MAPK inhibitors for the treatment of inflammatory diseases and cancer. Expert Opin Investig Drugs 18:1893–1905. https://doi.org/10.1517/13543780903321490

Zhao H, Wei R, Wang L, Tian Q, Tao M, Ke J, Liu Y, Hou W, Zhang L, Yang J, Hong T (2014) Activation of glucagon-like peptide-1 receptor inhibits growth and promotes apoptosis of human pancreatic cancer cells in a cAMP-dependent manner. Am J Physiol Endocrinol Metab 306:E1431–E1441. https://doi.org/10.1152/ajpendo.00017.2014

Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, Xue H, Liu Y, Zhang Y (2021) GLP-1 receptor agonists: beyond their pancreatic effects. Front Endocrinol (Lausanne) 12:721135. https://doi.org/10.3389/fendo.2021.721135

Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C, Gao J (2024) Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther 9:234. https://doi.org/10.1038/s41392-024-01931-z

Zhu XX, Feng ZH, Liu LZ, Zhang Y (2021) Liraglutide suppresses the proliferation of endometrial cancer cells through the adenosine 5'-monophosphate (AMP)-activated protein kinase signaling pathway. Chin Med J (Engl) 134:576–578. https://doi.org/10.1097/CM9.0000000000001363