AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2025, Vol. 9(2):e70143

DOI: 10.1002/oto2.70143
http://oto-open.org
WILEY

Targeting Stearoyl-CoA Desaturase 1 Through PI3K-AKT-mTOR Signaling in Head and Neck Squamous Cell Carcinoma

Cheng-Ming Hsu, MD, PhD[1,2,3], Ming-Yu Yang, PhD[4,5], Shun-Fu Chang, PhD[6], and Hui-Chen Su, MD[7,8]

Abstract

Objective. Stearoyl-coenzyme A desaturase 1 (SCD1) is a key enzyme in fatty acid metabolism and has been implicated in cancer progression, including head and neck squamous cell carcinoma (HNSCC). The phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) signaling pathway is a critical regulator of cellular metabolism and survival in cancer. This study investigates the crosstalk between SCD1 inhibition and the PI3K-AKT-mTOR pathway, highlighting the therapeutic potential of targeting SCD1 in HNSCC.

Study Design. Basic science.

Setting. Laboratory.

Methods. Four HNSCC cell lines were utilized to evaluate the relationship between SCD1 and the mTOR signaling pathway. Cell viability was assessed following treatment with various mTOR inhibitors. The effect of AKT-mTOR signaling on SCD1 expression was examined through pharmacological inhibition and gene silencing approaches. Additionally, the impact of SCD1 knockdown on cell proliferation and survival was analyzed.

Results. mTOR inhibitors significantly reduced HNSCC cell viability and downregulated SCD1 expression in a dose-dependent manner. Inhibition of AKT, a key upstream effector of mTOR, also suppressed SCD1 expression, suggesting that SCD1 is regulated through the PI3K-AKT-mTOR axis. Silencing SCD1 independently impaired cancer cell growth and enhanced the cytotoxic effects of mTOR inhibitors, indicating a synergistic anticancer effect.

Conclusion. SCD1 is a downstream target of the PI3K-AKT-mTOR pathway and contributes to HNSCC cell survival. Dual targeting of SCD1 and the mTOR signaling pathway represents a promising therapeutic strategy for HNSCC treatment. Further investigation is warranted to explore the clinical potential of SCD1 inhibitors in combination with mTOR-targeted therapies.

Keywords

head and neck squamous cell carcinoma (HNSCC), lipid metabolism, PI3K-AKT-mTOR signaling, stearoyl-CoA desaturase 1 (SCD1), therapeutic target

Received April 2, 2025; accepted May 31, 2025.

Cancers are characterized by heightened metabolic activity, leading to enhanced cell proliferation and survival.[1] Unlike normal cells, cancer cells exhibit metabolic autonomy, absorbing nutrients and metabolizing them at an accelerated rate to sustain rapid growth. However, the molecular mechanisms underlying the upregulation of fatty acid synthesis in cancer cells remain poorly understood. Key enzymes involved in fatty acid and lipid biosynthesis, such as adenosine triphosphate citrate lyase, acetyl-CoA carboxylase, and fatty acid synthase, are transcriptionally upregulated in tumors. This upregulation boosts the synthesis of saturated fatty acids (SFAs), which are subsequently converted into monounsaturated fatty acids (MUFAs).[2,3] Elevated levels of MUFAs have been detected in various cancerous tissues.[4]

Stearoyl-coenzyme A desaturase 1 (SCD1) is a pivotal enzyme located in the endoplasmic reticulum (ER), playing a crucial role in the de novo synthesis of fatty

[1]Department of Otolaryngology–Head and Neck Surgery, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan
[2]School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[3]Department of Otolaryngology–Head and Neck Surgery, Xiamen Chang Gung Hospital, Hua Qiao University, Xiamen, China
[4]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[5]Department of Otolaryngology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[6]Department of Medical Research and Development, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan
[7]Department of Neurology, National Cheng-Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[8]Chewing and Swallowing Center, National Cheng-Kung University Hospital, College of Medicine, National Cheng-Kung University, Tainan, Taiwan

Corresponding author:
Hui-Chen Su, MD, Department of Neurology, National Cheng-Kung University Hospital, No. 138, Sheng Li Road, Tainan 70101, Taiwan.
Email: shjmirage@gmail.com

acids. SCD1 catalyzes the introduction of the first double bond at the cis-9 position of saturated fatty acyl-CoAs, such as palmitoyl-CoA and stearoyl-CoA.[5] This rate-limiting step generates MUFAs, including palmitoleoyl-CoA and oleoyl-CoA, which serve as substrates for polyunsaturated fatty acid (PUFA) synthesis.[6] Consequently, SCD1 directly influences the SFA-to-MUFA ratio, a critical factor in maintaining membrane fluidity and cellular homeostasis. An imbalance in this ratio is associated with various pathological conditions, including cancer and metabolic disorders.

SCD1 is overexpressed in several cancers, including gastric,[7] colon,[8] prostate,[9] lung,[10] breast,[11,12] and hematologic malignancies.[13] During cancer progression, SCD1 expression is regulated by multiple oncogenes, transcription factors, and signaling pathways, highlighting its central role in cancer biosynthesis and tumorigenesis.

The phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway is one of the most frequently dysregulated signaling cascades in cancers, including head and neck squamous cell carcinoma (HNSCC).[14] This pathway is integral to regulating cell cycle progression, apoptosis, and proliferation,[15,16] making it a promising target for anticancer therapies. Despite extensive research on the PI3K-AKT-mTOR pathway, the relationship between this pathway and SCD1 expression remains elusive.

Therefore, this study aimed to investigate the crosstalk between SCD1 inhibition and the PI3K-AKT-mTOR signaling pathway in HNSCC. We examined the effects of pharmacological and genetic inhibition of SCD1 on pathway activity, cellular proliferation, and survival in HNSCC cell lines and explored the potential of SCD1 as a therapeutic target.

Methods

Patients and Samples

This study enrolled nine patients (eight males and one female) aged 45 to 72 years (mean ± standard deviation: 54.8 ± 8.6 years) who were diagnosed with HNSCC and underwent surgery at the Department of Otolaryngology, Chiayi Chang Gung Memorial Hospital, between 2004 and 2009. Tumor samples and adjacent noncancerous tissues were collected immediately after resection, snap-frozen in liquid nitrogen, and stored until RNA extraction. Informed consent was obtained from all patients before tissue acquisition. This study was approved by the Institutional Review Board of Chiayi Chang Gung Memorial Hospital (IRB No. 202400267B0C502).

Real-Time Quantitative Polymerase Chain Reaction

Total RNA was extracted from tumor samples and adjacent noncancerous tissues using the RNeasy Mini Kit (Qiagen). Complementary DNA (cDNA) synthesis was performed using the RevertAid First Strand cDNA Synthesis Kit (#K1622, Thermo Fisher Scientific). The expression levels of *SCD1* and *GAPDH* genes were measured using SYBR® Green. The primer sequences for the human *SCD1* gene were as follows—forward: 5′-AAA CCT GGC TTG CTG ATG-3′ and reverse: 5′-GGG GGC TAA TGT TCT TGT CA-3′. The primer sequences for the reference gene *GAPDH* were forward: 5′-GTC TCC TCT GAC TTC AAC AGC G-3′ and reverse: 5′-ACC ACC CTG TTG CTG TAG CCA A-3′. Each 20-μL reaction contained 50 ng of cDNA, 200 nM of each primer, and 10 μL of iQ SYBR Green Supermix (Bio-Rad Laboratories Inc.). Quantitative polymerase chain reactions (qPCRs) were performed using the CFX Opus Real-Time PCR System (Bio-Rad Laboratories Inc.). Relative gene expression in tumor tissues was determined using the comparative Ct (ΔΔCt) method. *SCD1* expression in non-tumor tissues was set as the reference (normalized to 1), and expression levels in tumor tissues were calculated as fold changes relative to the non-tumor counterparts.

Cell Culture

Four human HNSCC cell lines, SCC-4, SCC-25, FaDu, and Detroit 562, were used in this study. All cell lines were purchased from the Food Industry Research and Development Institute and underwent routine validation along with mycoplasma testing. They are passaged only once from frozen stocks. SCC-4 and SCC-25 cells were cultured in Dulbecco's modified Eagle medium and Ham's F12 (DMEM/F12) medium (Invitrogen) supplemented with 2.5 mM L-glutamine (Invitrogen), 400 ng/mL hydrocortisone (Sigma-Aldrich), and 10% fetal bovine serum (FBS, Invitrogen). FaDu cells were maintained in minimum essential medium (MEM) Eagle medium (Invitrogen) supplemented with 0.1 mM nonessential amino acids (NEAA, Invitrogen), 1.0 mM sodium pyruvate (Invitrogen), and 10% FBS (Invitrogen). Detroit 562 cells were cultured in MEM medium with 2 mM L-glutamine, 0.1 mM NEAA, 1.0 mM sodium pyruvate, 0.1% lactalbumin hydrolysate (all from Invitrogen), and 10% FBS. All cell lines were maintained at 37°C in a humidified atmosphere with 5% CO_2.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide Assay

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate the effects of different mTOR inhibitors on cell growth, including NVP-BEZ235 (dual PI3K and mTOR inhibitor), rapamycin (mTOR inhibitor), and LY294002 (PI3K inhibitor). SCC-4, SCC-25, FaDu, and Detroit 562 cells were treated with various concentrations of mTOR inhibitors or phosphate-buffered saline (PBS) as a control. The percentage of metabolically active cells was determined based on the mitochondrial reduction of

MTT into formazan crystals. For the assay, 5000 cells/well in 100 μL of culture medium were plated in triplicate in 96-well plates and treated with the inhibitors. After incubation, the culture medium was replaced with phenol red-free medium containing 0.02% MTT (Sigma-Aldrich). Following a 3-hour incubation at 37°C, the medium was carefully removed, and 100 μL of dimethyl sulfoxide (DMSO) (Sigma-Aldrich) was added to dissolve the formazan crystals. Absorbance was measured at 570 nm using the DTX880 Multimode Detector (Beckman Coulter). The viability of PBS-treated control cells was set as 100%, and the relative cell viability of treated cells was calculated accordingly. Statistical data are presented as the mean ± standard error of the mean (SEM) of duplicated samples from three independent experiments. Comparisons between control and treated samples were performed using an unpaired two-tailed Student's *t* test, with statistical significance set at $P < .05$.

Western Blot Analysis

Cells treated as described in each experiment were lysed in RIPA buffer (#89901, Thermo Fisher) supplemented with protease inhibitors. A total of 20 to 30 μg of protein from the cell lysates was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride membranes (Millipore) using electrophoretic transfer. Membranes were blocked with 5% skim milk in Tris-buffered saline with 0.1% Tween-20 (TBST) for 1 hour at room temperature, followed by overnight incubation at 4°C with the indicated primary antibodies. After three washes with TBST, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (anti-rabbit IgG #7074, anti-mouse IgG #7076, Cell Signaling Technology) for 1 hour at room temperature. Protein signals were detected using enhanced chemiluminescence and visualized with the Gel Doc 2000 system (Bio-Rad). The following primary antibodies were used: SCD1 (#2438), Phospho-AKT (Ser473) (#9271), and Phospho-mTOR (Ser2448) (#2971) from Cell Signaling Technology and actin (#sc-47778) from Santa Cruz Biotechnology.

Gene Silencing

To perform gene silencing using small interfering RNA (siRNA), cells were seeded in a culture dish 1 day before transfection to achieve 70% to 90% confluence at the time of transfection. siRNA was diluted in Opti-MEM (Thermo Fisher Scientific, catalog #319085062), whereas the transfection reagent Lipofectamine 2000 (Thermo Fisher Scientific, catalog #11668019) was separately diluted in the same buffer. The diluted siRNA and transfection reagent were combined and incubated at room temperature for 5 to 20 minutes to allow complex formation. The cell culture medium was replaced with fresh medium before the siRNA complexes were added dropwise to the cells. Cells were then incubated at 37°C in a CO_2 incubator for 24 to 48 hours. Gene silencing efficiency was evaluated by qPCR and Western blot.

Transwell/Migration Assays

Invasion of SCC-4, SCC-25, Fadu, and Detroit 562 cells was measured using 24-well Transwell chambers (Corning Incorporated) with 8.0-μm pore polycarbonate membrane filters covered with gelatin package. The bottom membrane of the Transwell chamber (8-μm aperture) was coated with Matrigel (Sigma-Aldrich), and the lower chamber was filled with 600 μL of DMEM containing 10% FBS. In total, 5×10^5 cells (200 μL) were inoculated in the upper chamber.

After incubation at 37°C, 5% CO_2 for 48 hours, the wells were removed and then fixed (methanol:glacial acetic acid, 3:1), stained with 0.1% crystal violet, and mounted.

The upper side of the membrane needs to be gently wiped with a cotton swab to gently remove cells and gel in the upper compartment of the insert. The inserts were completely dried, and the number of cells on the lower side of the filter was counted under a microscope.

Statistical Analyses

All values are presented as means ± SEM of replicate samples (n = 3-6, depending on the experiment), with all experiments repeated at least three times. Differences between groups were analyzed using an unpaired two-tailed Student's *t* test or one-way analysis of variance, depending on the number of groups. A *P* value < .05 was considered statistically significant. Statistical analyses were performed using SPSS version 15.0 software (SPSS).

Results

Patients With HNSCC Exhibit Higher SCD1 Expression

To assess SCD1 expression in tumor tissues, we conducted quantitative reverse transcription-PCR analysis on paired tumor and non-tumor tissues from nine HNSCC patients. The results revealed a significant upregulation of SCD1 expression in tumor tissues ($P = .003$) (**Figure 1**).

mTOR Inhibitors Suppress Head and Neck Cancer Cell Growth

We investigated the antiproliferative effects of three mTOR inhibitors, NVP-BEZ235, rapamycin, and LY294002, on SCC-4, SCC-25, FaDu, and Detroit 562 cell lines using the MTT assay. SCC-4 and SCC-25 are both oral squamous cell carcinoma cell lines derived from the tongue; FaDu is a hypopharyngeal squamous cell carcinoma cell line; Detroit 562 is an oropharyngeal adenocarcinoma cell line. After 72 hours of treatment, each inhibitor demonstrated distinct inhibitory effects on cell growth (Figures 2A-C). Specifically, NVP-BEZ235, rapamycin, and LY294002 significantly inhibited cell growth at concentrations of 2.5, 20, and 30 μM, respectively.

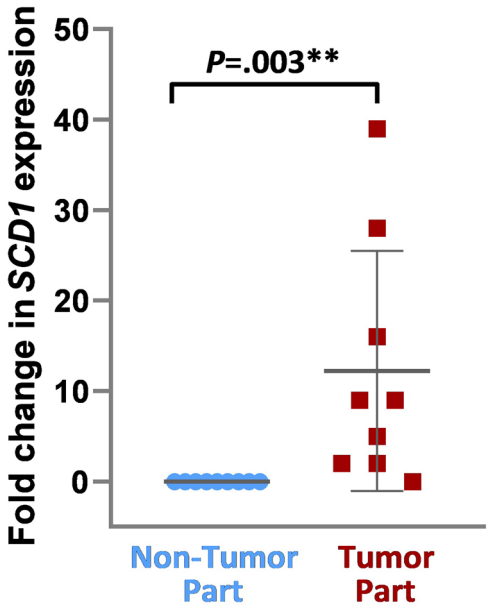

Figure 1. Stearoyl-coenzyme A desaturase 1 (SCD1) expression in head and neck squamous cell carcinoma (HNSCC). SCD1 expression was significantly upregulated in tumor tissues of HNSCC (n = 9, *P* = .003). The *y*-axis represents the fold change in SCD1 expression levels.

Notably, LY294002, a nonselective PI3K inhibitor, failed to inhibit FaDu cell growth (**Figure 2C**).

mTOR Inhibitors Suppress SCD1 Expression

To assess the impact of mTOR inhibitors on SCD1 expression, NVP-BEZ235, rapamycin, and LY294002 were administered to SCC-4, SCC-25, FaDu, and Detroit 562 cells. NVP-BEZ235, which targets both AKT and mTOR, demonstrated strong inhibition of AKT across all four cell lines, with full inhibition of SCD1 expression achieved after 24 hours (**Figure 3A**). Rapamycin, an mTOR inhibitor that does not inhibit AKT, also led to significant SCD1 suppression within 24 hours (**Figure 3B**). LY294002 produced similar effects, effectively reducing SCD1 expression in a dose-dependent manner (**Figure 3C**).

AKT Activation Enhances and Inhibition Reduces SCD1 Expression

To investigate whether AKT activation enhances SCD1 expression, SC79, an AKT-specific activator, was applied to SCC-4, SCC-25, FaDu, and Detroit 562 cells. SC79-induced AKT hyperphosphorylation led to increased

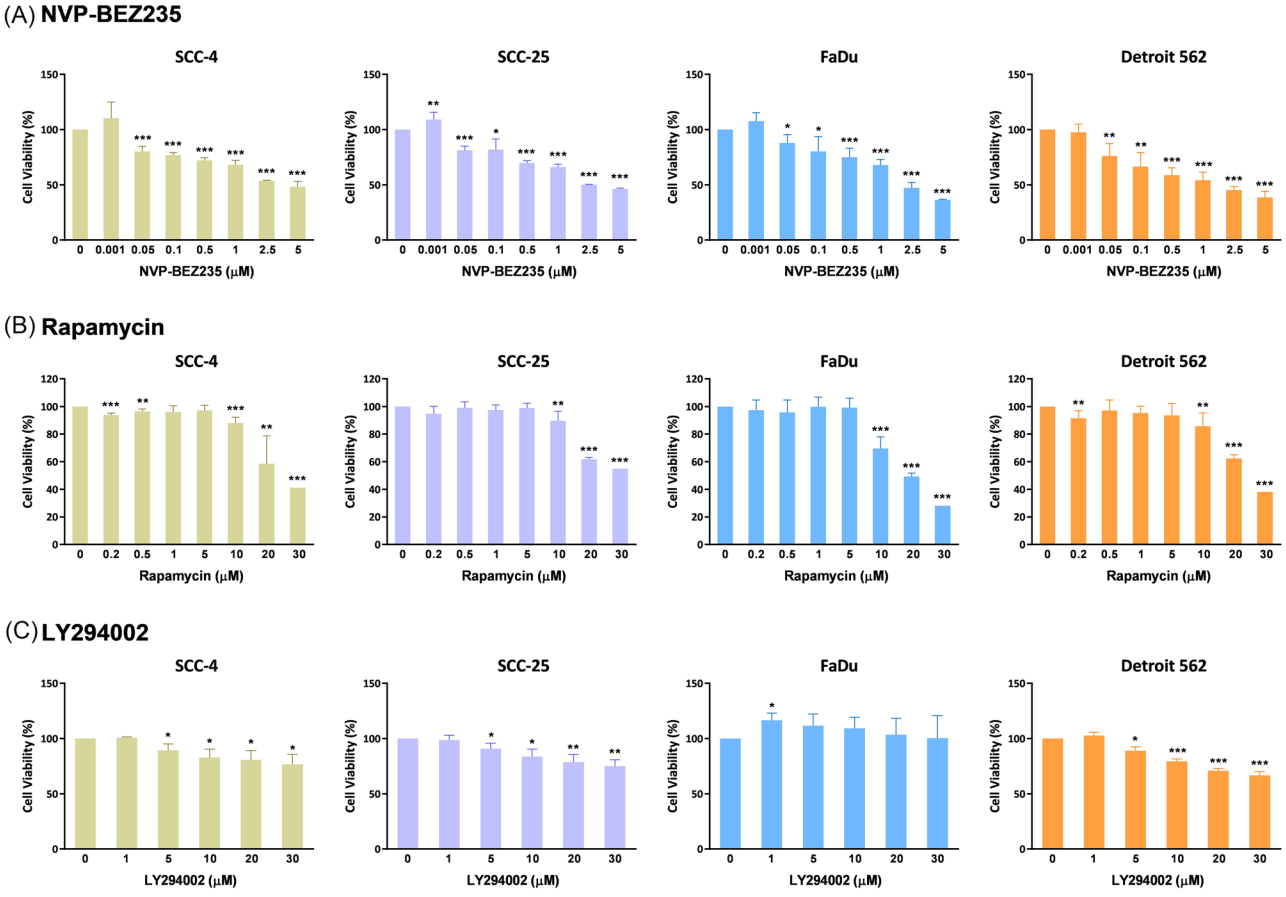

Figure 2. Inhibitory effects of (A) NVP-BEZ235, (B) rapamycin, and (C) LY294002 on head and neck squamous cell carcinoma cell viability in a dose-dependent manner, measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. **P* < .05, ***P* < .01, and ****P* < .001 compared to untreated control cells.

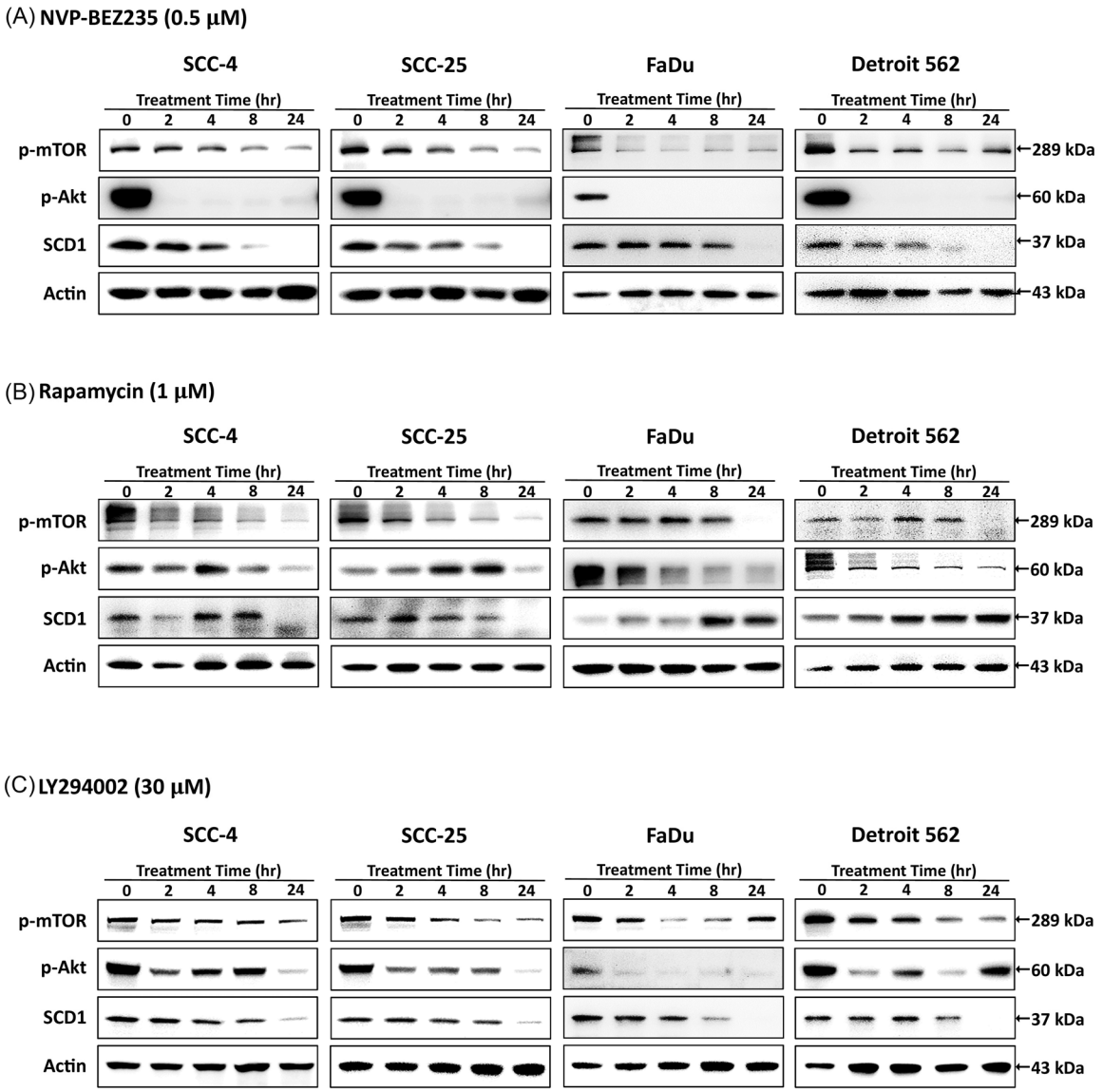

Figure 3. Stearoyl-coenzyme A desaturase 1 (SCD1) expression following treatment with three mammalian target of rapamycin (mTOR) inhibitors. Treatment with (A) NVP-BEZ235, (B) rapamycin, and (C) LY294002 for 24 hours exhibited varying inhibitory effects on SCD1 expression across four head and neck squamous cell carcinoma cell lines.

SCD1 expression in a dose-dependent manner in SCC-4 and Detroit 562 cells (**Figure 4A**). However, this effect was not significant in SCC-25 and FaDu cells. The increase in SCD1 expression was accompanied by elevated p-AKT and p-mTOR levels.

Conversely, the effects of AKT inhibition on SCD1 expression were assessed using Capivasertib (AZD5363), a selective pan-AKT kinase inhibitor. AZD5363 significantly reduced SCD1 expression in SCC-4, SCC-25, and Detroit 562 cells, but not in FaDu cells (**Figure 4B**). The reduction in SCD1 expression was dose-dependent and correlated with decreased mTOR activity.

SCD1 Silencing Inhibits HNSCC Proliferation and Migration

To elucidate the role of SCD1 in cell proliferation and migration, transient knockdown of SCD1 was performed in SCC-4, SCC-25, FaDu, and Detroit 562 cells. MTT assays revealed a significant reduction in proliferation at 72 hours post-knockdown, particularly in FaDu ($P = .038$) and Detroit 562 cells ($P = .014$) (**Figure 5A**). Additionally, after 48 hours of incubation in transwell chambers, all four cells exhibited reduced migratory and invasive capacities in siSCD1-treated groups compared to siControl-treated cells (**Figure 5B**). Data represent the mean ± SEM from three independent experiments (*$P < .05$ compared to control).

Discussion

Our study yielded several pivotal findings. First, we systematically evaluated the effects of three mTOR inhibitors on SCD1 expression in various HNSCC cell lines. Although prior research has shown that mTOR

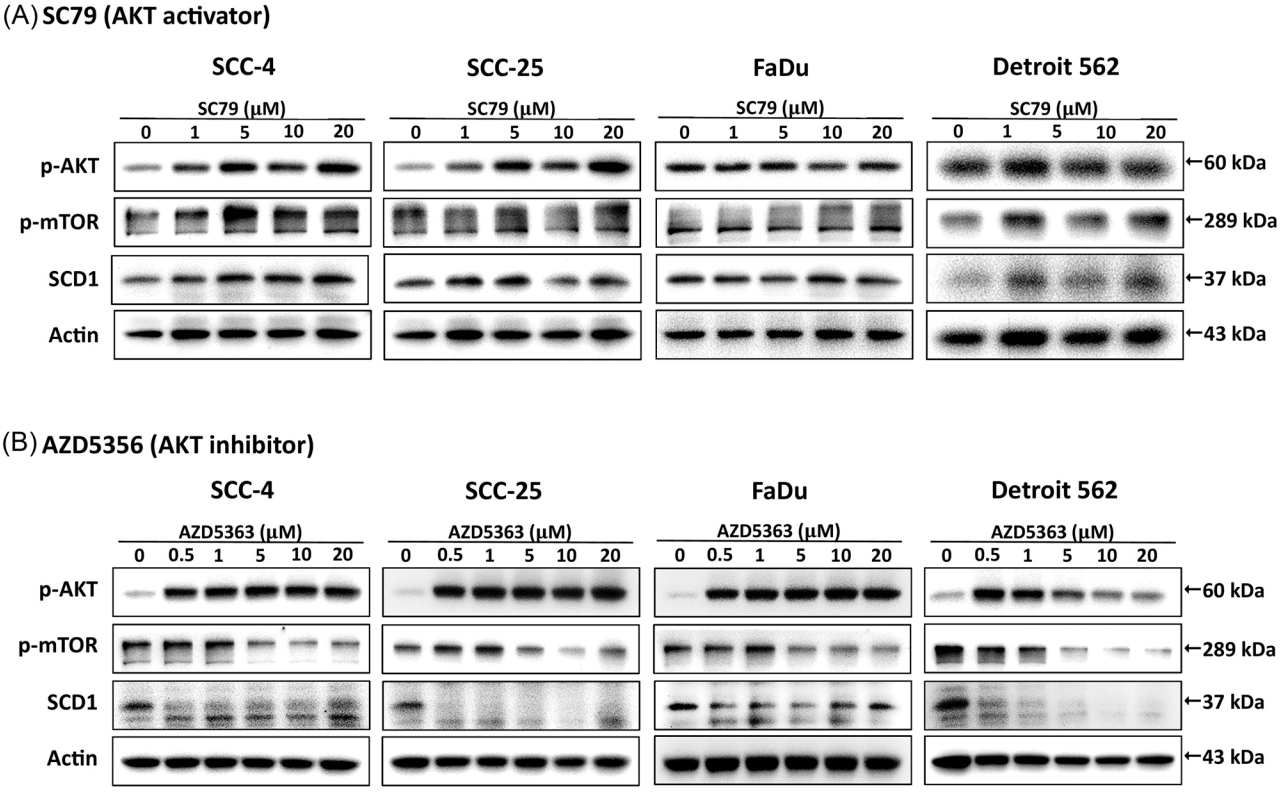

Figure 4. Regulation of stearoyl-coenzyme A desaturase 1 (SCD1) by AKT signaling. (A) SC79 activates AKT, increasing SCD1 and p-mammalian target of rapamycin (mTOR) in SCC-4 and Detroit 562 cells. (B) AZD5363 inhibits AKT, reducing SCD1 and p-mTOR in HNSCC cells.

inhibitors affect cancer cell proliferation, our study uniquely highlights the diverse effects of these inhibitors on SCD1 regulation. Notably, NVP-BEZ235, a dual inhibitor of AKT and mTOR, effectively reduced SCD1 expression across all tested cell lines, an observation not extensively analyzed in previous studies. Additionally, SC79, an AKT activator, significantly increased SCD1 expression in certain HNSCC cell lines, revealing a regulatory link between the AKT/mTOR pathway and SCD1. Furthermore, Capivasertib (AZD5363) effectively inhibited both SCD1 expression and mTOR activity, a finding that expands on existing literature.

Our findings also emphasize the role of SCD1 silencing in decreasing the proliferation and migration of HNSCC cells, particularly in FaDu and Detroit 562 cells. This contrasts with earlier studies that focused primarily on the AKT and mTOR pathways. Our results suggest that targeting SCD1 could be a promising therapeutic strategy, especially in tumors with high SCD1 expression levels.

The mTOR signaling pathway is a key regulator of lipid and protein metabolism and plays a dominant role in cancer formation. Upon AKT activation, mTOR is phosphorylated, leading to downstream effects on cellular proliferation and metabolism. This pathway is crucial in regulating the cancer cell cycle, mitosis, and apoptosis through various genetic pathways.[17] In HNSCC, mTOR hyperactivation is a significant factor,[18] with the majority of cases associated with genomic alterations due to mTOR deregulation.[19] Moreover, mutations in genes like EGFR, PIK3CA, and PTEN are commonly observed in the PI3K-AKT-mTOR pathway in HNSCC.[20-22]

The PI3K/AKT pathway is vital in tumor initiation, progression, and the development of precancerous conditions. Our experiments demonstrate that NVP-BEZ235 and rapamycin exhibit superior cytotoxicity compared to LY294002, affirming the critical role of the mTOR pathway in HNSCC growth. Modulating AKT or mTOR activity significantly impacts SCD1 expression, with mTOR inhibitors markedly reducing HNSCC cell line growth.

SCD1 serves as a potential therapeutic target in malignancies due to its high expression in various cancers and its role in controlling fatty acid metabolism and cellular functions, including ER stress signaling and tumor pathways such as Wnt/β-catenin.[23-25] SCD1 promotes cancer cell proliferation, tumor growth, and metastasis and is a prognostic indicator. Our study shows that silencing SCD1 reduces HNSCC cell proliferation and migration. Factors like glucose, acetyl-CoA, and the tumor microenvironment upregulate SCD1, whereas caloric restriction, a ketogenic diet, and AMPK downregulate it.[26] SCD1's role in lipid biosynthesis and metabolism makes it a promising target for cancer therapy. Its expression correlates with cancer aggressiveness in liver,[27] thyroid,[28] prostate,[29] pancreatic,[30] kidney,[31] and breast[32] cancers. Inhibition of SCD1 expression significantly reduces tumor size in preclinical models,[33] supporting its potential as a therapeutic target.

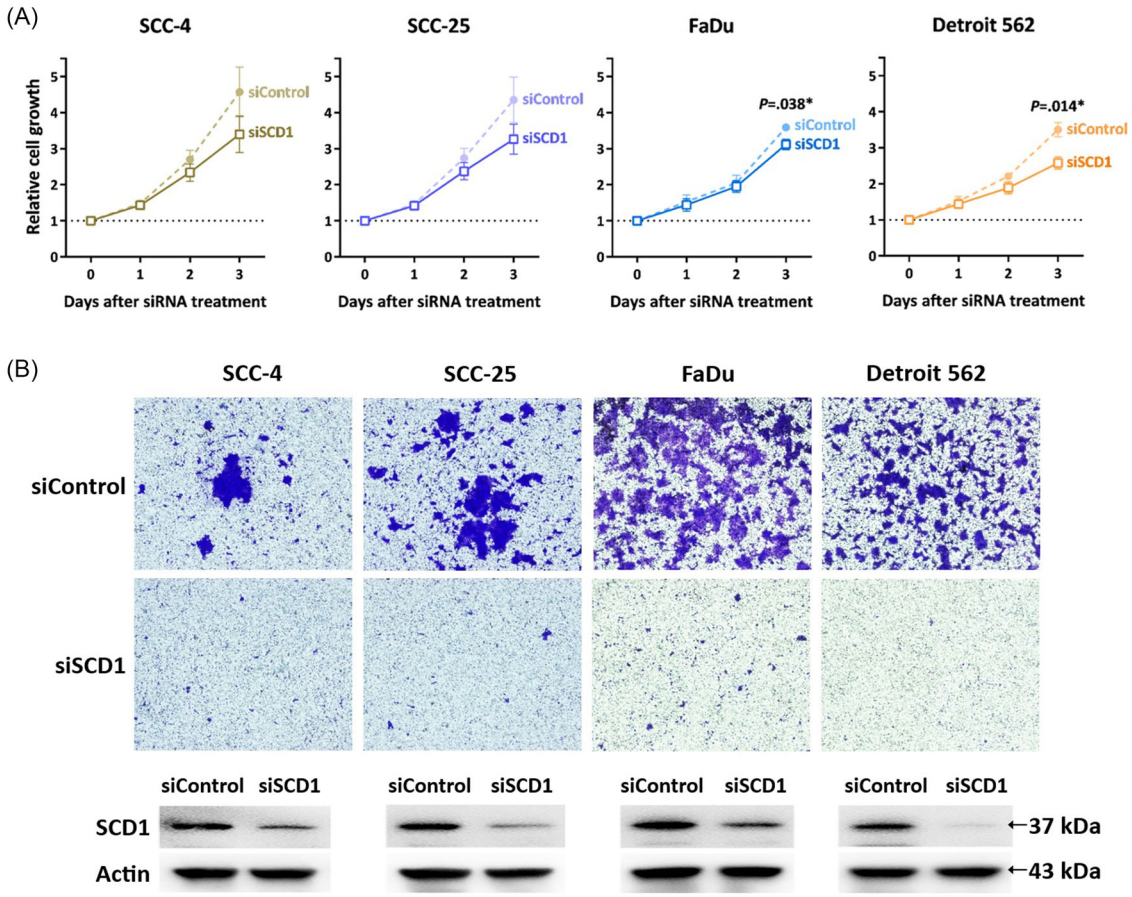

Figure 5. Stearoyl-coenzyme A desaturase 1 (SCD1) silencing inhibits head and neck squamous cell carcinoma (HNSCC) progression. (A) Reduced proliferation in FaDu and Detroit 562 by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. (B) Decreased migration and invasion in HNSCC cells. *$P < .05$ compared to control cells. siRNA, small interfering RNA.

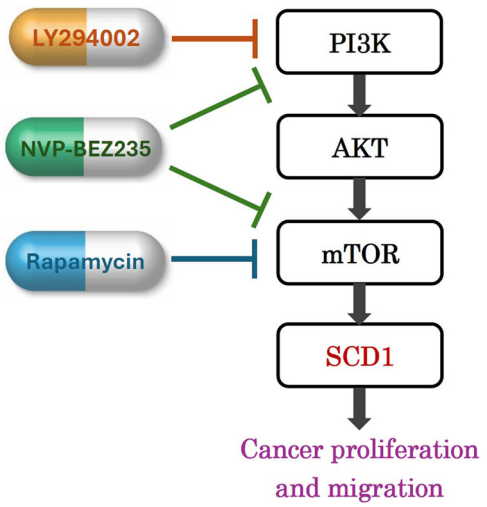

Figure 6. Graphical summary of the mechanism of cancer apoptosis by inhibiting the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)/stearoyl-coenzyme A desaturase 1 (SCD1) axis.

The link between SCD1 and the mTOR pathway remains underexplored. In clear cell renal cell carcinoma, SCD1 expression correlates with disease severity through the PI3K-AKT-mTOR pathway.[34] However, the relationship between SCD1 and autophagy in cancer cells is controversial, as autophagy can have dual effects depending on lipid response.[5] Our study demonstrates that (1) inhibiting SCD1 expression can be achieved with both AKT and mTOR inhibitors, which also suppress cancer cell growth in HNSCC, and (2) silencing SCD1 reduces cell proliferation in HNSCC cells. The potential regulatory relationship between SCD1 and the AKT/mTOR pathway is illustrated in **Figure 6**.

Limitations of this study include the absence of gene knockout methods to confirm SCD1 function, a lack of animal experiments to validate tumor growth, and an insufficient exploration of SCD1's upstream and downstream pathways.

Conclusions

Our study demonstrates that SCD1 expression plays a vital role in the survival and apoptosis of HNSCC and is associated with the proliferation of HNSCC cell lines via the PI3K-AKT-mTOR pathway. These findings highlight the importance of lipid metabolism in HNSCC and suggest that inhibiting SCD1 through mTOR pathway inhibition may represent a novel therapeutic approach.

Author Contributions

Cheng-Ming Hsu, Conceptualization; writing—review and editing; project administration; funding acquisition. **Ming-Yu Yang**, Methodology; writing—review and editing; supervision. **Shun-Fu Chang**, Methodology. **Hui-Chen Su**, Writing—original draft preparation; supervision.

Disclosures

Competing interests: The authors declare no conflict of interest.

Funding source: This research was funded by Chang Gung Memorial Hospital (grant numbers CMRPG6L0261, CMRPG 6L0471, CMRPG6M0361, CMRPG6L0271, CMRPG6L0272, and CMRPG6L0273) and the National Science and Technology Council, Taiwan (grant number NSTC 112-2314-B-182-013-MY3).

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

ORCID iD

Cheng-Ming Hsu https://orcid.org/0000-0003-3792-3784
Ming-Yu Yang https://orcid.org/0000-0002-6841-5478
Shun-Fu Chang https://orcid.org/0000-0002-2276-7785
Hui-Chen Su https://orcid.org/0000-0002-1482-8664

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