RESEARCH ARTICLE

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Therapeutic Targeting of S100A2 Enhances Chemotherapy Efficacy *in vitro* in Oral Cancer

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Abstract

Objective: Despite advancements in multimodal therapies, oral squamous cell carcinoma (OSCC) continues to exhibit poor clinical outcomes, particularly in advanced and recurrent cases. Recent studies have identified the calcium-binding protein S100A2 as a critical mediator of OSCC progression and resistance to therapy. Our prior work demonstrated that cytoplasmic overexpression of S100A2 in oral cancer patients is associated with tumor recurrence and reduced survival. Given its reported role in promoting epithelial-to-mesenchymal transition (EMT), cellular proliferation, and invasiveness, we investigated the in vitro functional impact of S100A2 inhibition in OSCC. **Methods:** Silencing S100A2 significantly impaired tumor cell proliferation and enhanced apoptotic cell death, as evidenced by Annexin V and caspase-3 activation. **Results:** Notably, S100A2-deficient OSCC cells exhibited increased sensitivity to chemotherapeutic agents, including carboplatin, 5-fluorouracil, paclitaxel, and doxorubicin, through mitochondrial apoptotic pathways. **Conclusion:** These findings position S100A2 as a potential therapeutic target for overcoming drug resistance and improving treatment efficacy in OSCC. Further mechanistic studies and in vivo validation are warranted to explore its translational relevance in clinical oncology.

Keywords: Oral cancer- chemotherapy- S100A2- therapeutic resistance- Epithelial mesenchymal transition

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Introduction

Oral cancer represents about 5% of global cancers but roughly 30–40% of cancers in India, reflecting a disproportionate burden linked mainly to tobacco and related habits. GLOBOCAN 2022 reports that approximately 15 per 100,000 men and 5 per 100,000 women in India are diagnosed with it. It is the most prevalent cancer in Indian men and ranks fourth among women, after breast, cervical, and ovarian cancers [1]. In India, the National oral cancer registry estimates nearly 60,000 new cases of oral cancer each year, highlighting a major public health issue, especially in Southeast Asia [2]. About two-thirds of OSCC cases are diagnosed at advanced stages, significantly affecting clinical outcomes. In OSCC, patient mortality is largely driven by tumor invasion, lymph node metastasis, locoregional recurrence, and the development of second primary tumors [3, 4]. Despite advancements in surgical and radiotherapeutic techniques, the prognosis for individuals with advanced or recurrent OSCC remains poor, with five-year survival rates below 50% [4-6]. Chemotherapy regimens like cisplatin, carboplatin, docetaxel, and 5-fluorouracil (5-FU) are key to treatment, but their effectiveness is often hindered by systemic toxicity and therapeutic resistance [7]. Molecular targeted therapies have emerged as a promising strategy to tackle these challenges in recent years. Identifying reliable and effective molecular targets is crucial, particularly for advanced and recurrent OSCC [8]. Our previous proteomic studies identified the calcium-binding protein S100A2 as a potential biomarker for OSCC, with elevated expression levels associated with poorer prognosis and a possible role in oral carcinogenesis [9]. S100A2 plays diverse roles in several cancer types, including oral, esophageal, lung, endometrial, pancreatic, gastric, and colorectal cancers [9-16]. S100A2, a member of the S100 protein family, controls several biological processes involved in tumor progression such as cell proliferation, apoptosis, metastasis, and tumor microenvironment interactions, suggesting it could act as an oncogenic factor in multiple cancers. Additionally, S100A2 may serve as a valuable target to improve chemotherapy effectiveness in OSCC. Yet, its precise molecular role in OSCC remains unclear. So, the present study explores S100A2's role in oral carcinogenesis and evaluates its potential as a therapeutic target to enhance chemosensitivity. Understanding the

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molecular mechanisms regulated by S100A2 may provide insights into OSCC pathogenesis and aid in developing more effective targeted treatments.

Materials and Methods

Reagents

All chemicals and antibodies were available commercially designed short hairpin RNA (shRNA) targeting S100A2 was constructed in pSilencer Eukaryotic shRNA expression vector. Lipofectamine 2000 and Opti-MEM for transfection were from Invitrogen; rabbit monoclonal anti-S100A2 antibody (0.5 µg/ml, [EPR5392] (ab109494, Abcam, CA); and mouse monoclonal glyceraldehyde-3-phosphate dehydrogenase [ab8245] (Anti-GAPDH antibody [6C5]), Annexin V assay kit (ab14084), was from Abcam; carboplatin (Sigma-232120), 5-Fluoro Uracil (Sigma-F6627), paclitaxel (Sigma-580555), doxorubicin (Sigma-D1515), propidium iodide (PI) (Sigma-537060),MTT (Sigma-475989), and DMSO (Sigma-D4540) were from Sigma; Caspase 3 assay kit (G8091) was from Promega, (USA).

Cell culture and transfection

The SCC-4 cell line, a human oral squamous cell carcinoma line, was obtained from the American Type Culture Collection (ATCC), which authenticates cell lines using short tandem repeat (STR) polymorphism analysis. The cells were used within six months of resuscitation to ensure optimal performance. SCC-4 cells were cultured as a monolayer in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1 mmol/L L-glutamine, , 100 µg/mL streptomycin, and 100 U/mL penicillin. Cultures were maintained at 37°C in a humidified atmosphere containing 5% CO_2 and 95% air, following established protocols [17]. To generate S100A2 knockdown cells, a eukaryotic pSilencer shRNA expression vector targeting S100A2 (shS100A2) was constructed. Transfection of SCC4 cells was performed using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. Briefly, 2×10^5 SCC4 cells were seeded in each well of a six-well plate 24 hours prior to transfection. The following day, cells were transfected with the pSilencer shS100A2 plasmid. After 48 hours, cells were trypsinized and transferred to T-25 flasks containing selection medium supplemented with 2 mg/mL puromycin. Continuous selection pressure resulted in significant cell death among transfected populations. Puromycin-resistant colonies were isolated and individually expanded in 24-well plates until they reached approximately 70% confluence, after which they were transferred to T-25 flasks and maintained in puromycin-containing media throughout the study. Five stable SCC4 clones expressing shS100A2 (designated shS100A2-1 to shS100A2-5) were established and screened for S100A2 downregulation relative to parental SCC4 cells (Supplementary Figure S1). The clone exhibiting the most effective knockdown (shS100A2-1) was selected for further experiments.

Western blot analysis

Equal amounts of whole-cell lysates prepared from the SCC-4and SCC4-S100A2S1 cells were subjected to Western blotting. Briefly, equal amounts of proteins (50µg) from cells were resolved on SDS-polyacrylamide gels. The proteins were then electro transferred onto nitrocellulose membranes (Bio-Rad). After blocking with 5% nonfat powdered milk in TBS (0.1 mol/L, pH 7.4), the blots were trimmed beyond the gel boundaries and incubated with anti-S100A2 or GAPDH antibody at 4°C overnight. Membranes were incubated with secondary antibody, horseradish peroxidase–conjugated rabbit/ mouse anti-IgG (Bio-Rad), diluted at an appropriate dilution in 1% non-Fat milk, for 2 hours at room temperature. After each step, blots were washed three times with 0.1% Tween–TBS. Protein bands were detected by the enhanced chemiluminescence method (GE Healthcare) on Kodak hyper film as described earlier [17]. Changes in protein levels were determined by densitometric scanning of the immunoreactive bands. Quantifications of S100A2 protein bands were carried out by calculating Integrated Density Values and normalizing it against total GAPDH levels. This normalization accounted for differences in protein loading and transfer efficiency, allowing comparison of relative S100A2 expression levels across conditions. Immunoblotting for each protein was done at least in triplicate using independently prepared lysates. Blots were imaged and analyzed in the Chemi Doc™ imaging system from Bio-Rad.

Cell proliferation assay

SCC4 and SCC4S100A2S1 were plated in quadruplicate in 96-well plates in complete medium. The cells were cultured overnight and then treated to varying concentrations of one of the chemotherapeutic agents: carboplatin (1–200 µM/L), 5-FU (5–500 µM/L), paclitaxel (0.5–50 µM/L), or doxorubicin (5–100 µM/L) for 48 hours to determine dose- and time-dependent inhibition of cell proliferation. Cell proliferation was measured by adding MTT at 37°C for 3 to 4 hours. The formazan crystals were dissolved in 100µL of DMSO, and the absorbance (A) was measured at a wavelength of 570 nm. The percentage cell proliferation was calculated individually for each doses follows: (Acontrol−Atreated/Acontrol) × 100, as described earlier [17].

Cell death analysis using flow cytometry

SCC4 and SCC4-S100A2S1 control cells were subjected for CT-treatment or no treatment at 48 hours interval. The cultured media were collected from treated or untreated centrifuged to collect nonadherent cells. Adherent cells were washed with PBS (pH 7.4) and trypsinised. Both nonadherent and adherent cell populations were pooled for further analysis. Cells were fixed in 70% ethanol (−20°C, overnight) and resuspended in buffer containing PBS (pH 7.4), EDTA (0.5 mol/L, pH 8.0), Triton X-100 (0.05%), RNase A (50 µg/mL), and PI (100 µg/mL) before flow cytometric analysis. The PI-labeled cells were analyzed using a BD Canto flow cytometer, and the output thus obtained was analyzed using the BD Diva Pro software. Cells were gated to

exclude cell debris and cell clumps. Annexin V and PI dual staining was used to quantify apoptosis. SCC4 and SCC4S100A2S1 CT-treated and untreated control cells (SCC4) were collected as described above. Cells were labeled with Annexin V–FITC conjugate and PI using the Annexin V assay kit following the manufacturer's instructions (BD Bioscience) and analyzed using the BD Diva Pro software.

Statistical analysis

Statistical analysis of the data was carried out using the SPSS 21.0 software (Chicago). Statistical significance was determined using the paired two-tailed Student's t test. A probability $P \leq 0.05$ was considered to be statistically significant.

Results

Knockdown of S100A2 expression reduce the cell proliferation in oral cancer cells

To determine the necessity of S100A2 for cell proliferation, we established a stable S100A2 knockdown cell line (SCC4-S100A2S1) in SCC4 oral cancer cells. The effectiveness of the S100A2 knockdown was confirmed using a specific monoclonal antibody against S100A2 (Abcam, CA) (Figure 1A). We employed the MTT assay, a widely accepted method for assessing cell viability and proliferation. Our results demonstrated a significant suppression of cell proliferation upon S100A2 knockdown, highlighting its critical role in sustaining OSCC cell growth (Figure 1B).

Knockdown of S100A2 gene enhances the efficacy of chemotherapeutic agents to oral cancer cells

To assess the dose-dependent effects of various chemotherapeutic agents on cell viability, SCC4 parental cells and S100A2 knockdown SCC4-S100A2S1 cells were treated with increasing concentrations of carboplatin (1–200 μM), 5-fluorouracil (5-FU; 10–500 μM), paclitaxel (0.1–50 μM), and doxorubicin (10–200 μM) for 48 hours. A marked reduction in cell viability was observed in SCC4-S100A2S1 cells compared to control SCC4 cells across all tested drugs. Paclitaxel (Taxol) treatment led to a progressive decline in cell viability, with SCC4-S100A2S1 cells displaying significantly higher sensitivity at all concentrations tested (Figure 2A). A similar pattern was observed with doxorubicin, where SCC4-S100A2S1 cells demonstrated notably reduced viability in a dose-dependent manner relative to SCC4 control cells (Figure 2B). Consistent trends were seen

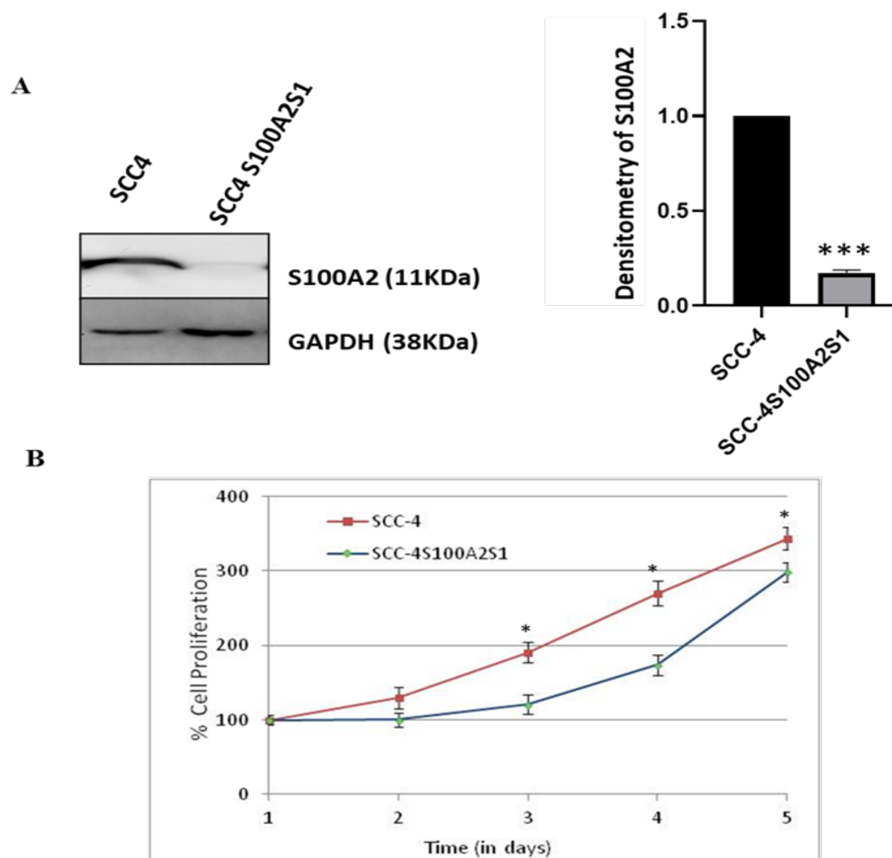

Figure 1A and B. A). A. Confirmation of S100A2 knockdown in SCC4 cells. (Left) Representative western blot showing reduced S100A2 protein expression in SCC4 cells transfected with S100A2 siRNA compared with control cells. β-actin was used as a loading control. (Right) Densitometric quantification of S100A2 protein levels normalized to GAPDH, demonstrating effective knockdown efficiency. B. Cell proliferation analysis using MTT assay in SCC4 (control) and SCC4-shS100A2S1 cells. Cells were seeded in 96-well plates in quadruplicate, and MTT assays were performed at 24-hour intervals. Percent proliferation was quantified and plotted as mean ± SD from three independent experiments, each performed in quadruplicate. Statistical significance was determined using a paired t-test. Asterisks (*) indicate values significantly different ($p < 0.05$) from SCC4 control cells. Knockdown of S100A2 resulted in a significant reduction in proliferation, indicating a potential role for S100A2 in regulating oral cancer cell growth.

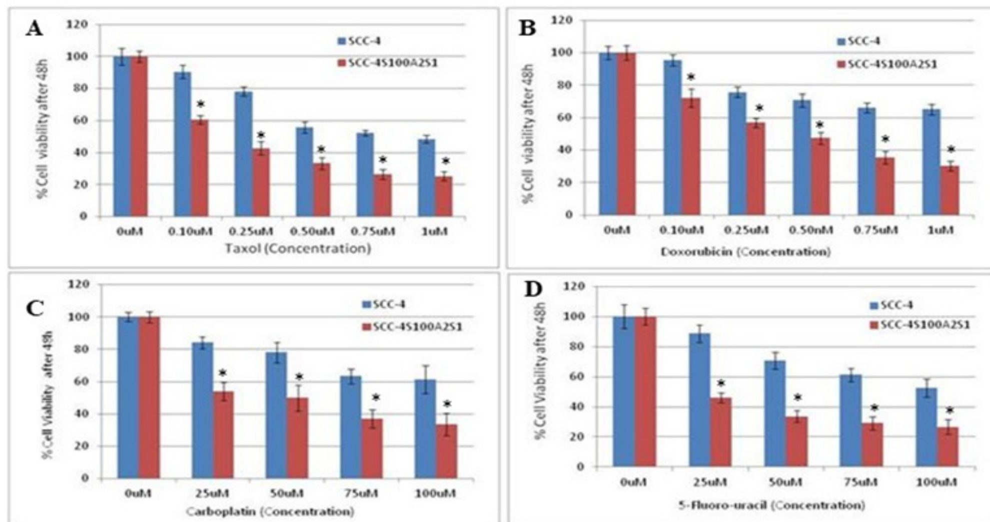

Figure 2 (A to D). Cells were treated with increasing concentrations of carboplatin (A), 5-fluorouracil (5-FU) (B), doxorubicin (C), and taxol (D) for 48 hours. Post-treatment, cell viability was assessed using MTT assays. Data represent mean ± SD from three independent experiments, each performed in quadruplicate. S100A2 downregulation significantly increased the chemosensitivity of SCC4 cells, with approximately a twofold reduction in across all drugs. Notably, for taxol decreased from 0.8 μM in SCC4 cells to 0.2 μM in SCC4-shS100A2S1 cells (4.0-fold increase in sensitivity), and for doxorubicin, from 0.9 μM to 0.35 μM (2.57-fold increase). These findings strongly suggest that S100A2 silencing enhances the responsiveness of oral cancer cells to standard chemotherapeutic agents.

with carboplatin and 5-FU, both of which induced a concentration-dependent decrease in viability, with knockdown cells exhibiting enhanced chemosensitivity compared to their parental counterparts (Figure 2C, 2D).

Importantly, untreated control SCC4 cells maintained stable viability throughout the experiment, indicating that the observed chemo-sensitization was specifically associated with reduced S100A2 expression. These results suggest that S100A2 knockdown significantly enhances the cytotoxic effects of conventional chemotherapeutic agents in OSCC cells.

Decreased S100A2 expression and subsequent chemotherapeutic drug treatment induces apoptosis in oral cancer cells

To evaluate the role of S100A2 in modulating chemotherapeutic-induced apoptosis in oral cancer cells, we performed Annexin V-FITC/PI staining followed by flow cytometric analysis in SCC4 parental cells and S100A2 knockdown SCC4-S100A2S1 cells. Following treatment with chemotherapeutic agents, SCC4-S100A2S1 cells exhibited a significant increase in apoptotic cell populations compared to SCC4 control cells (Figure 3). This finding suggests that downregulation of S100A2 enhances the pro-apoptotic effects of chemotherapy in OSCC cells.

To further corroborate these results, caspase-3 activity assays were conducted. Consistent with Annexin V data, SCC4-S100A2S1 cells demonstrated significantly elevated caspase-3 activity in response to all chemotherapeutic treatments tested. Notably, the increase in caspase-3 activity was particularly pronounced following treatment with paclitaxel and doxorubicin (Figure 4). SCC4-S100A2S1 cells (green bars) consistently showed higher caspase-3 activation compared to SCC4 cells (blue bars), indicating robust induction of apoptosis in the S100A2-deficient background.

Collectively, these findings confirm that S100A2 knockdown sensitizes OSCC cells to chemotherapeutic agents by enhancing apoptotic pathways. Consistent findings from Annexin V and caspase-3 assays underscore the critical role of S100A2 in regulating apoptosis, and highlight its potential as a therapeutic target to improve the efficacy of chemotherapy in oral cancer.

Discussion

Oral squamous cell carcinoma (OSCC) remains a major clinical challenge because of its high recurrence rate and few treatment options in advanced stages [3–6]. Conventional therapies provide limited benefits, and therapeutic resistance along with tumour progression frequently results in poor patient outcomes. There is a growing focus on identifying molecular factors that contribute to disease aggressiveness and treatment failure [4-7]. This study emphasises S100A2's key role in influencing the growth and chemoresistance of OSCC cells, suggesting its potential as a therapeutic target to improve conventional chemotherapy effectiveness. In this study achieving stable S100A2 knockdown in SCC4 cells caused a marked reduction in cell proliferation, underscoring the essential role of S100A2 in OSCC cell growth. These findings align with earlier studies identifying S100A2 as a multifunctional calcium-binding protein that acts as both a tumour promoter and suppressor, depending on the cellular context.

Our data demonstrate that reduced expression of S100A2 significantly sensitises OSCC cells to multiple chemotherapeutic agents, including paclitaxel, doxorubicin, carboplatin, and 5-fluorouracil (5-FU).

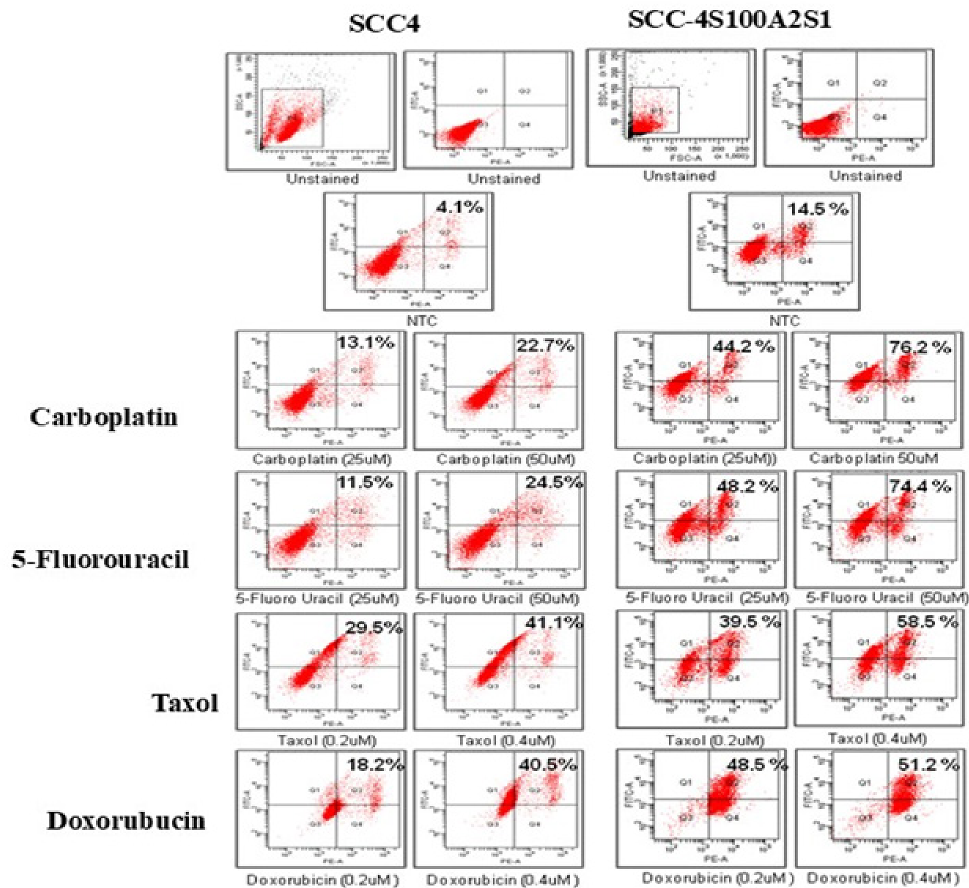

Figure 3. Assessment of Apoptosis in SCC4 and SCC4-S100A2S1 Oral Cancer Cell Lines Following Chemotherapeutic Treatment. SCC4 and SCC4-S100A2S1 cells (6×10^4 cells/well) were seeded in six-well plates. After 24 hours, cells were serum-starved in 1% FBS-containing DMEM for 6 hours to synchronize them. Subsequently, cells were treated with sub-lethal doses of selected chemotherapeutic drugs for 48 hours. Apoptosis was quantified using flow cytometry following staining with FITC-conjugated Annexin V and propidium iodide (PI). The proportion of apoptotic cells was compared between control and S100A2-silenced cells to evaluate the effect of S100A2 downregulation on drug-induced apoptosis.

Across all drug treatments, SCC4-S100A2S1 cells exhibited enhanced chemosensitivity relative to parental SCC4 cells, as evidenced by reduced viability in a dose-dependent manner. Among the tested agents, paclitaxel and doxorubicin showed the most pronounced cytotoxic effects in the S100A2-deficient background. These results suggest that S100A2 confers a survival advantage to OSCC cells under chemotherapeutic stress, potentially

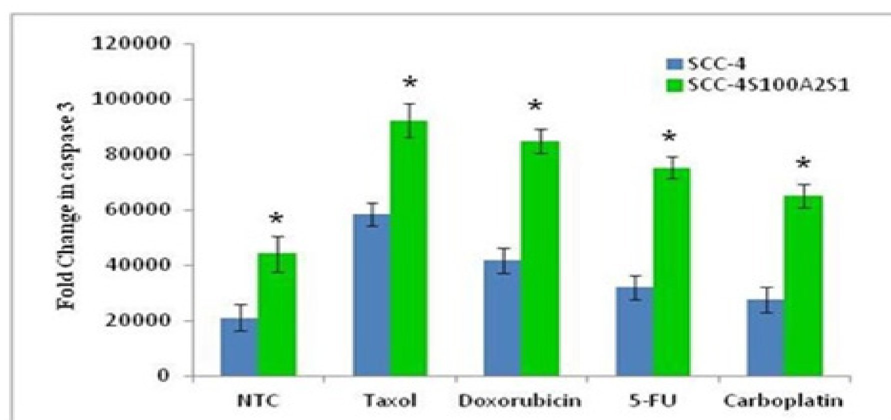

Figure 4. Effect of S100A2 Down Regulation and Chemotherapeutic Drugs on caspase-3: SCC4-S100A2S1 and SCC-4 cells after treatment with taxol, doxorubicin, 5-FU and carboplatin for 48 hours were lysed with Apo-GloTM buffer followed by assaying Caspase-3 activity using a Luminometer. Untreated cells were processed identically and served as controls. Values expressed are mean ± SD of at least three independent experiments performed in triplicates. Values significantly different from the control have been marked by ‘*’ ($p<0.05$).

through mechanisms involving drug resistance and inhibition of apoptotic signaling.

Importantly, mechanistic investigation revealed that knockdown of S100A2 substantially enhances apoptosis upon chemotherapeutic exposure, as shown by increased Annexin V/PI-positive populations and elevated caspase-3 activity. This indicates that S100A2 may negatively regulate apoptosis, thereby limiting the efficacy of anticancer agents. In SCC4-S100A2S1 cells, increased caspase-3 activation, particularly after paclitaxel and doxorubicin treatment, indicates that S100A2 knockdown may lower the apoptotic threshold in OSCC cells, thereby enhancing chemotherapy's cytotoxic effects.

These observations align with emerging evidence that S100 family members are involved in diverse cellular processes, including proliferation, differentiation, and apoptosis [16, 18-22]. Although S100A2 has traditionally been considered a tumor suppressor in certain cancers, its role in OSCC appears to be more complex [16]. Our findings suggest a context-dependent oncogenic function, wherein S100A2 supports OSCC cell survival and drug resistance, possibly through modulation of redox signaling, p53 interaction, or mechanistically activated the transforming growth factor (TGF)-β/Smad2/3 signaling pathway mediated epithelial–mesenchymal transition (EMT) [19, 20]. Recent studies have shown that knocking down S100A2 significantly inhibits EMT, invasion, migration, and metastasis of PDAC cells in both in vitro and in vivo models, accompanied by a decrease in SMAD4 expression; contrarily, upregulation of SMAD4 promoted EMT and enhanced metastasis in PANC-1 cells [20]. These findings align with previous research showing that inhibiting S100A2 can block TGF-β1-induced EMT by suppressing the β-catenin signaling pathway in A549 cells [21]. However, a major limitation of our study is that we were unable to conduct a colony-forming assay, which could have offered further corroboration and strengthened the validation of our results. This study highlights S100A2 as a key modulator of chemotherapeutic response in oral squamous cell carcinoma (OSCC), demonstrating that its inhibition enhances the efficacy of standard chemotherapy. While initially described as a tumor suppressor, S100A2 has shown oncogenic behavior in several cancers. Overexpression has been linked to poor prognosis in oral [9], cervical [10], esophageal [11], lung [12], endometrial cancer [13], pancreatic [14], Gastric [15] and colorectal cancers [16] the latter also showing associations with immune infiltration [16]. Additionally, S100A2 has been shown to promote tumor progression via diverse pathways, including GLUT1-mediated glycolysis in nasopharyngeal carcinoma [23] and Wnt/β-catenin-driven EMT in pulmonary fibrosis [24].

S100A2's role may be connected to a fundamental cellular pathway like the regulation of stress responses, apoptosis, or other essential survival mechanisms that is broadly impacted by various therapeutic agents, rather than being restricted to a drug-specific resistance function. In support of our findings recent studies demosntrated that knocking down S100A2 reduces aggressive cellular behavior in endometrial cancer, and also identifies S100A2 as a potential therapeutic target in colorectal cancer [25, 26]. These findings reinforce the concept that S100A2 is involved in a common, central regulatory mechanism that governs cellular responses to multiple treatments. Silencing S100A2 reduced the viability, migration, and invasion of endometrial cancer cells, and significantly suppressed tumor growth in vivo. Additionally, its knockdown activates anti-tumor immunity through the STING pathway in endometrial cancer [25]. Recent emerging evidence highlights S100A2 as a promising therapeutic target in cancer. In colorectal cancer, S100A2 forms a complex with KPNA2 to mediate NFYA nuclear translocation, leading to E-cadherin repression and enhanced metastasis. Targeting the S100A2/KPNA2 interaction with delanzomib disrupts this axis, restores E-cadherin expression, and suppresses tumor progression [26]. These findings support the role of S100A2 as a context-dependent oncogene, and our results position it as a potential therapeutic target and prognostic marker in OSCC. Knocking down S100A2 in SCC4 cells increases their sensitivity to various chemotherapeutic agents, suggesting that combining S100A2 inhibition with standard chemotherapy could enhance tumor cell apoptosis, lower drug dosages, and potentially reduce systemic toxicity.

Further investigation is required to clarify the molecular mechanisms behind the chemo-sensitization of oral cancer cells after S100A2 knockdown, marking a primary limitation of this study, which emphasizes phenotypic effects. Future studies should pinpoint S100A2's upstream regulators and downstream targets, while validating results in suitable in vivo models, to fully delineate its influence on chemotherapy responses in OSCC.

This study identifies S100A2 as a key regulator of OSCC proliferation and shows that its presence is linked to sensitivity to various chemotherapeutic drugs. Targeted downregulation of S100A2 not only impairs tumor cell growth but also enhances the pro-apoptotic efficacy of multiple chemotherapeutic agents. These findings provide a strong rationale for the development of S100A2-targeted therapies as an adjunct to existing treatment regimens for oral cancer.

Author Contribution Statement

S.S.C., C.P., and M.K. conceived and directed the study. M.K. generated the stable knockdown cell lines. M.K. C.P., S.T. and C.P. performed the in vitro experiments, processed the data, and analyzed the results. S.S.C. C.P., S.T. and M.K. analyzed the experimental data. The study was initiated by S.S.C. and M.K., and subsequently continued by M.K. C.P., S.T. and C.P. The manuscript was initially drafted by M.K., S.S.C and finalized with input from all authors.

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Any conflict of interest

The authors do not have any conflict of interest.

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