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# Stearoyl-CoA Desaturase-1 (SCD1) inhibition as a potential therapeutic strategy for targeting lung cancer stem cells

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**Abstract**

Lung cancer stem cells (CSCs) are highly resistant to current therapy methods, which leads to a high likelihood of cancer relapse. The aim of this study was to investigate whether the enzyme Stearoyl-CoA Desaturase-1 (SCD1) plays a role in mediating the reactive oxygen species (ROS) resistance in CSCs derived from the A549 lung adenocarcinoma cell line. In our experiments, CSCs were cultured, and their stem cell identity was confirmed via marker analysis. Saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) were quantified using liquid chromatography–mass spectrometry (LC-MS). SCD1 expression was assessed through quantitative real-time PCR analysis and western blotting. Our results showed that CSCs expressed significantly higher levels of MUFAs and SCD1 in comparison to bulk A549 cells. Based on these findings, we employed SCD1 inhibitors in the medicinal assay. We found increased CSCs death following treatment with SCD1 inhibitors in combination with ROS inducers (Tert-butyl hydroperoxide and hydrogen peroxide). These findings suggest that SCD1 contributes to ROS resistance and cell survival in lung cancer and indicate that targeting SCD1 could potentially be used as a therapeutic method to enhance ROS-based cancer treatments. Further studies could investigate SCD1's role *in vivo* and its potential in combination with other treatment methods.

**Keywords**

Gene inhibition, Stearoyl-CoA Desaturase-1, Cancer Stem Cells, Lung cancer, Reactive Oxygen Species, A549 cell line, Adenocarcinoma, SCD1 inhibitor, Cancer resistance, Mono Unsaturated Fatty Acids

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## 1 Introduction

Lung cancer makes up 1 in 5 of cancer deaths (1,2). Early metastasis accounts for the poor prognosis in patients with lung cancer. The 5-year survival rate of patients with lung cancer is marginally (21%), greater than other types of cancer (3). The recurrence is mainly due to the development of Cancer Stem Cells (CSCs) that are drug or therapy-resistant. It is, therefore, crucial to focus on treatment modality to overcome the resistance of cancer stem cells and improve the prognosis for patients with lung cancer.

Radiation therapy is one of the major treatment methods for lung cancer. It induces reactive oxygen species (ROS), which break cells' DNA strands and increase base oxidation, which is detrimental to the survival of cancer cells (4). However, due to the lung cancer stem cells' resistance, treatments including radiation therapy or chemotherapy are less effective. Thus, it is important to understand the resistance mechanisms in cancer stem cells to clarify how they acquire ROS resistance.

Stearoyl-CoA desaturase-1 (SCD1), which catalyzes the introduction of a cis-double bond into saturated fatty acyl-CoAs to generate monounsaturated fatty acids (MUFAs), is a key enzyme in fatty acid metabolism whose expression has been shown to increase the rate of cell proliferation (5). Studies show that the higher the expression of SCD1 in patients, the lower their survival rate (6). The poor recovery rate applies to patients with larger proportion of cancer stem cells and patients with high SCD1 expression. Therefore, this study investigated the hypothesis that it is because cancer stem cells have particularly high SCD1expression, that leads to low recovery rates and recurrences. To investigate the role of SCD1, A549 cells, representative of non-small cell lung carcinoma (NSCLC), specifically adenocarcinoma, which are widely used in lung cancer research, were used to culture and isolate CSCs.

## 2 Methods

### **2.1** Cells and culture conditions

The objective of this experiment was to compare lung bulk A549 (designated as Adh-A549) and lung CSCs (designated as Sph-A549). CSCs were cultured in serum-free DMEM/F12 medium with EGF (20 ng/mL), bFGF (10 ng/mL), and $N_2$ supplement for 10-12 days. Adherent bulk-A549 (Adh-A549) cells were cultured in F-12K medium supplemented with 10% Fetal Bovine Serum (FBS). The incubator was set to 37°C with 5% $CO_2$. These cells were cultured independently for the experiments in this research.

### **2.2** Lipid extraction and lipidomic analysis

Saturated Fatty Acids (SFAs) and MonoUnsaturated Fatty Acids (MUFAs) were analyzed using LC–MS. Mass spectrometry-based lipid analysis was performed by Lipotype GmbH (Dresden, Germany). We specifically analyzed the SFA and MUFA composition of glycerophospholipids (GPLs) and glycerolipids (GLs), the main substrate classes of SCD1.

### **2.3** RNA extraction and real-time Polymerase Chain Reaction (PCR) analysis

The total RNA of A549 cells was extracted by

the Illustra RNAspin mini kit (GE Healthcare, USA) according to the manufacturer's steps. The process included first synthesizing the RNA into the form of Complementary DNA (cDNA) using Arrow-Script Reverse transcriptase (ARROWTEC, Taipei, Taiwan). Next, the cDNA was used to run the real-time Polymerase Chain Reaction (PCR) analysis to find the relative mRNA expression of SCD-1 using SCD-1 primers. Lastly, the SCD-1 expresion was normalized to the expresison of GAPDH. The PCR was run on 3 other stem-cell markers, which were also normalized to GAPDH. The results were used to determine if the spheroid-A549 was a stem cell. The 3 stem-cell markers were NANOG, Oct4, and Sox2. The quantitative real-time PCR was performed using FastStart SYBR Green Master (Roche Applied Science, Germany) and an ABI StepOnePlus Real-Time PCR System machine (Applied Biosystems, USA).

**2.4** Western blot analysis

The A549 cell lysates were collected in a commercial lysis buffer (Corning, USA) and protease inhibitor cocktail. The samples went through the process of being loaded on 10% SDS-PAGE, then electrophoresed, and lastly transferred onto a PVDF membrane (PerkinElmer Life and Analytical Sciences, USA). To prevent non-specific binding, the membranes were blocked with 5 % milk (Bio-Rad, USA) in TBST (20 mM Tris–HCl, 137 mM NaCl, 1% Tween 20) for 1 hour at room temperature. Subsequently, the membranes were incubated overnight at 4 °C with the first antibodies: SCD-1 (1:2000) (ab236868; Abcam, UK), Actin (1:5000) (20536-1; Proteintech, USA). The next morning, the membranes were incubated with HRP-labeled secondary antibodies for another hour at room temperature. After running the membranes through 2 antibodies, a chemiluminescent system (PerkinElmer) was used to record the signals, which were then exposed to X-ray film to visualize the protein bands (Amersham Pharmacia Biotech, Inc., USA).

**2.5** Medicine evaluation and analysis

A cell viability assessment was performed to evaluate the effectiveness of each treatment. Cells were seeded in 96-well plates ($1 \times 10^4$ cells per well) overnight. The cells were then treated with Tert-butyl hydroperoxide (TBH; Sigma-Aldrich, USA), hydrogen peroxide ($H_2O_2$; Sigma-Aldrich) for 24 hours. These medications both produce ROS, which are effective in killing cancer cells. In addition, the cells were treated with sorafenib (20 μM; Sigma-Aldrich) for 24 hours, or with stearic acid (200 μM; Sigma-Aldrich) or oleic acid (50 μM; Sigma-Aldrich) for 48 hours. In the inhibitor groups, SCD1 inhibitor (Sigma-Aldrich) was administered at 1 μM for 24 or 48 hours. Next, 10 μL of CCK-8 solution was added and incubated at 37°C for 1 hour. Afterwards, the plate was measured at 450 nm using a Spectramax iD3 multi-mode microplate reader (Molecular Devices, USA) to obtain results on the effectiveness of the treatments.

**2.6** Statistical analysis

All data were reported as the means ± standard deviations. We employed the Student's two-tailed unpaired t-test for two groups and one-way ANOVA, by Tukey's post-hoc for more than three groups. Data with $p < 0.05$ were considered statistically significant and were

used in the results for consideration during discussion. *p < 0.05, **p < 0.01, ***p < 0.001.

## 3 Results

### 3.1 Spheroid-derived A549 cells show higher expression of cancer stem cell markers

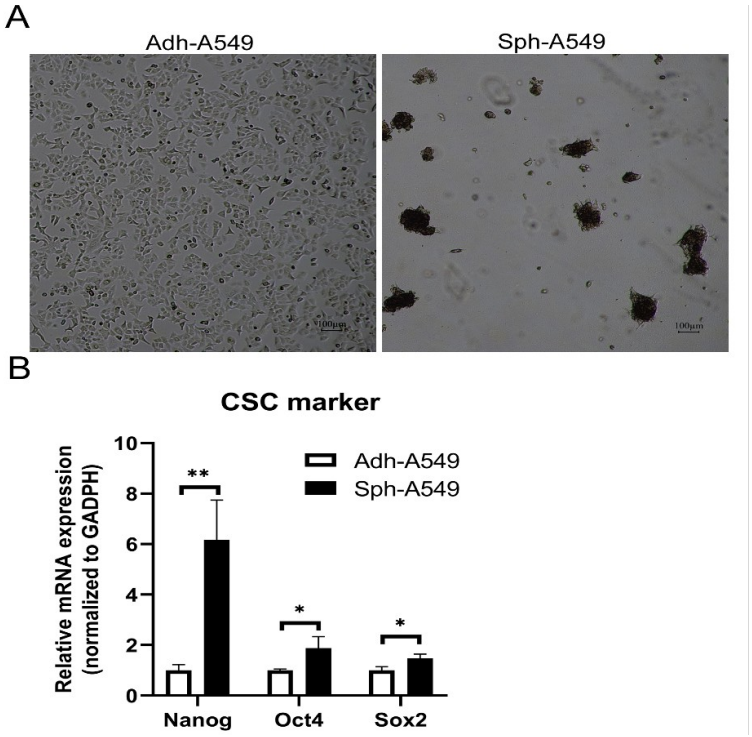


**Figure 1.** CSCs formation. (**A**) Scaled visualization of Adh-A549 and Sph-A549. (**B**) RNA expression of CSC markers between Adh-A549 and Sph-A549.

Cancer stem cells (CSCs) were enriched using spheroid culture. Sph-A549 (CSCs) and Adh-A549 (bulk A549 cells) differed in size and morphology, with Sph-A549 cells forming spherical structures (Figure 1A). Results from the PCR analysis indicated that the expression of CSC markers in Sph-A549 was significantly higher than in Adh-A549 (Figure 1B). These results support the identification of Sph-A549 cells as Cancer Stem Cells.

### 3.2 CSCs are resistant toward $H_2O_2$ and TBH induced cell death

The $H_2O_2$ was effective in killing Adh-A549 but only killed ~ 20% of the Sph-A549 at 1000 μM (Figure 2A). Furthermore, TBH was a more effective treatment and killed more than 50% of the Adh-549 at 500 μM, while Sph-A549 remained relatively resistant (Figure 2B). The increased efficacy of TBH is likely due to its greater stability, slower dissociation, and longer-lasting effects. These findings demonstrated the resistance of CSCs to ROS

treatment. This observation was consistent with clinical findings, as often stem cells do not respond well to ROS inducers, causing the recurrence of the disease.

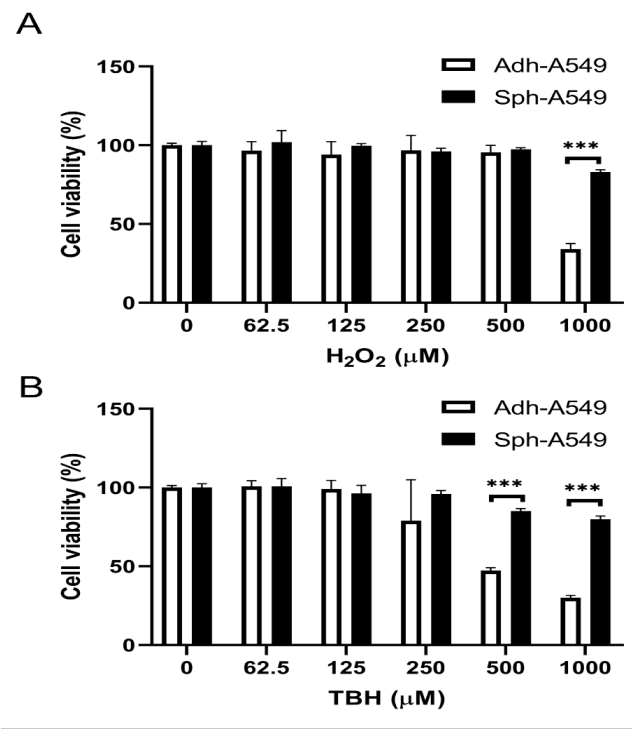


**Figure 2.** ROS resistance in CSCs. (**A**) Cell viability for different concentrations of $H_2O_2$ for Adh-A549 and Sph-A549. (**B**) Cell viability for different concentrations of TBH for Adh-A549 and Sph-A549.

**3.3** CSCs exhibit high RNA and protein expression levels of SCD1

SCD1 is an enzyme that catalyzes the introduction of a cis-double bond into saturated fatty acyl-CoAs, thereby generating monounsaturated fatty acids (MUFAs) (Figure 3A). To explore the relationship between SCD1 and ROS resistance, we first analyzed the percentage composition of saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) in Adh-A549 and Sph-A549. We then examined both RNA and protein levels of SCD1. Our results showed that Sph-A549 exhibited a higher MUFA content (Figure 3B) and almost 50% more mRNA expression of the *SCD1* gene (Figure 3C). The Western blot analysis results also showed a more prominent expression in Sph-A549 (Figure 3D). Collectively, these findings imply a potential role for SCD1 in supporting CSC properties that induce resistance and recurrance.

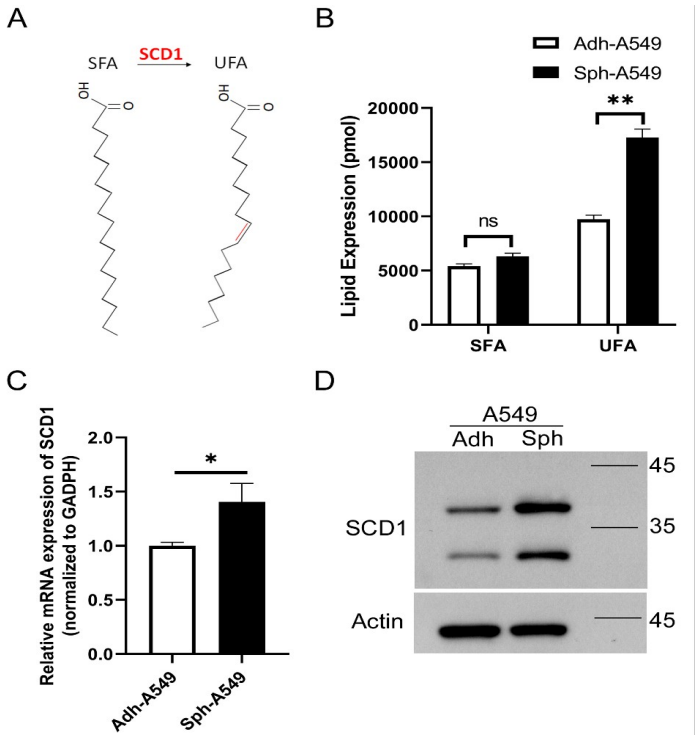


**Figure 3.** SCD1-mediated lipid desaturation is upregulated in CSCs. (**A**) Schematic illustration of the enzymatic function of SCD1. (**B**) Percentage composition of saturated fatty acids (SFAs) and unsaturated fatty acids in Adh-A549 and Sph-A549. (**C**) RNA expression of the *SCD1* gene in Adh-A549 and Sph-A549. (**D**) Protein expression of SCD1 in Adh-A549 and Sph-A549. After normalizing with actin, the expression of Sph-A549 was 2.6 times higher than Adh-A549.

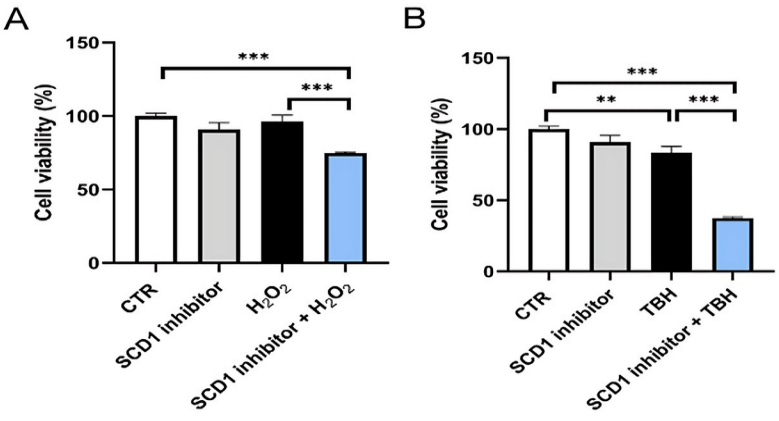


**Figure 4.** SCD1 increases the susceptibility of CSCs to ROS toxicity. (**A**) Cell viability after treatment with SCD1 inhibitor and $H_2O_2$ for Sph-A549. (**B**) Cell viability after treatment with SCD1 inhibitor and TBH for Sph-A549.

**3.4** CSCs are more susceptible to ROS-induced cell death after SCD1 inhibition

To further investigate the relationship between SCD1 and ROS resistance, we utilized an SCD1 inhibitor for validation. Significantly more Sph-A549 cells were killed following the treatment with $H_2O_2$ or TBH in combination with the SCD1 inhibitor (Figure 4). Additionally, the SCD1 inhibitor itself did not cause cell death. The findings of this experiment suggest that SCD1 expression is important for resistance to ROS in CSCs.

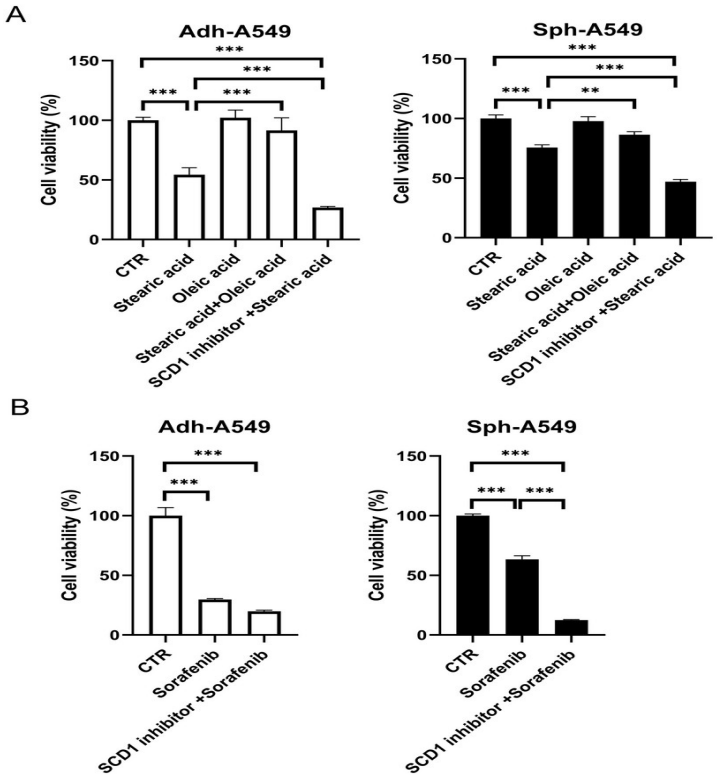


**Figure 5.** SCD1 regulates MUFA-dependent survival and ferroptosis in lung CSCs. (**A**) Cell viability after SCD1 inhibitor and stearic acid treatment. (**B**) Cell viability after SCD1 inhibitor and sorafenib treatment.

**3.5** SCD1 regulates MUFA-dependent survival and ferroptosis resistance in lung CSCs

SCD1 is a key enzyme for MUFA synthesis. To further investigate the importance of MUFAs in lung cancer cell survival, we treated cells with stearic acid to modulate MUFA levels. This treatment significantly reduced cell viability, with a more pronounced effect in Adh-A549 cells compared to Sph-A549 cells.

In contrast, supplementation with MUFAs, such as oleic acid, rescued cell survival. Moreover, the combination of an SCD1 inhibitor with stearic acid further enhanced the cytotoxic effect (Figure 5A). Additionally, we investigated the relationship between MUFAs

and ferroptosis in lung cancer. Sph-A549 cells were more resistant to sorafenib treatment. However, combining SCD1 inhibition with sorafenib resulted in pronounced cell death (Figure 5B). Collectively, SCD1 inhibition effectively sensitized CSCs to drug-induced cytotoxicity, suggesting that SCD1 regulates MUFA-mediated resistance in lung CSCs.

**3.6** SCD1 is a critical regulator of stemness in lung CSCs

To further investigate the role of SCD1 in stemness, we treated CSCs with an SCD1 inhibitor on days 1, 4, 7, and 11 during sphere culture. This treatment markedly suppressed sphere formation and reduced the expression of cancer stem cell markers (Figure 6). These findings suggest that SCD1 is a critical regulator of stemness.

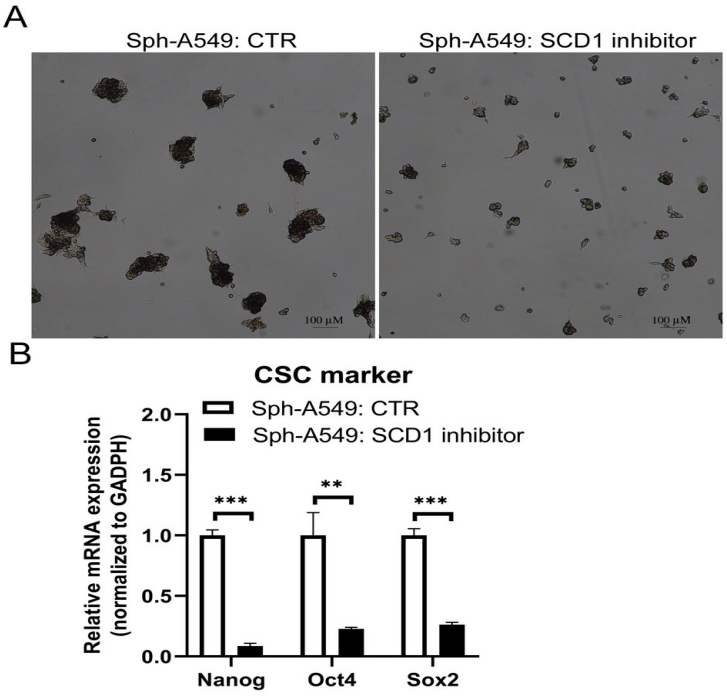


**Figure 6.** SCD1 inhibition reduces stemness in lung CSCs. (**A**) Sphere formation after SCD1 inhibition. (**B**) RNA expression of CSC markers following SCD1 inhibition.

## 4 Discussion

Previous research has highlighted the importance of SCD1 in cancer biology. For example, studies have shown that the gene SCD1 was essential for the maintenance of lung cancer cells and that its inhibition significantly reduced tumor growth in living organisms (5). The study conducted on living organisms reinforces the data presented in this study, which was performed at a cellular level. In addition, beyond lung cancer, SCD1 has been reported to be overexpressed in various other cancers, such as breast and liver cancer (6). Importantly, SCD1 was also closely

associated with CSCs. High expression of SCD1 promoted CSC proliferation, migration, and inhibited cell death, whereas SCD1 blockade reduced stemness, tumorigenesis, and metastasis (7-13). In this study, we demonstrated that SCD1 was associated with the resistance of lung CSCs to ROS. When the SCD1 inhibitor was added, lung CSCs became sensitive to $H_2O_2$ or TBH treatment. Moreover, it impaired their ability to form spheres and diminished their stemness. These data suggest that SCD1 is one of the deciding factors in lung cancer stem cells and may play a role in the prognosis of patients with lung cancer. Taken together, our findings are supported by other published studies, indicating that targeting SCD1 could represent a promising therapeutic strategy not only for lung cancer but potentially for other malignancies as well (14,15).

Additionally, recent literature has found that SCD1 inhibition increases the SFA to MUFA ratio, making cells more sensitive to apoptosis and impairing cancer cell viability (16). Another study further reported that a diet rich in stearic acid, when combined with SCD1 inhibition, inhibited tumorigenesis and blocked tumor formation (17). In our study on lung CSCs, we examined the effect of SCD1 inhibition in combination with stearic acid. The data demonstrated that stearic acid induced cell death, whereas oleic acid provided a rescue effect. Notably, combining SCD1 inhibition with stearic acid further enhanced cell death, consistent with the literature. Future studies should include detailed mechanistic investigations and *in vivo* models to further evaluate the therapeutic potential of combining SCD1 inhibitors with SFAs.

Previous studies (18-20) have shown that MUFA enrichment protects cancer cells against ferroptosis, whereas MUFA depletion sensitizes cells. In our study on lung CSCs, we found that combining SCD1 inhibition with a ferroptosis inducer such as sorafenib produced a more pronounced cytotoxic effect than combining SCD1 inhibition with ROS inducers. Specifically, sorafenib combined with SCD1 inhibition increased cell death by 50.9%, whereas the two ROS inducers, $H_2O_2$ and TBH combined with SCD1 inhibition increased cell death by 21.5% and 45.9%, respectively. These findings suggest that SCD1 inhibition diminishes MUFA-mediated protection and thereby sensitizes cells to ferroptotic death. Moreover, if combined SCD1 inhibition with simultaneous administration of stearic acid and ferroptosis inducers such as sorafenib proves effective, it could potentially reduce the need for subsequent radiation therapy, offering an advantage to patients by minimizing (radiation induced) collateral damage. Nonetheless, radiation therapy may still be necessary in certain contexts, particularly for eradicating resistant tumor subclones and reshaping the immune microenvironment (21). Therefore, combining SCD1 inhibition with radiation therapy could provide a comprehensive strategy to target both CSCs and resistant tumor cells.

Although SCD1 is an attractive target for cancer therapy, prolonged inhibition may be circumvented by mutations, reduced transcriptional expression that diminishes SCD1 dependency, or activation of alternative pathways such as FADS2 upregulation to preserve MUFA supply and thereby alleviate

ER-stress–induced cell death. To address these escape routes, co-inhibition strategies have been proposed, including simultaneous blockade of MUFA synthesis pathways, inhibition of lipid uptake, and sensitization of cells to ferroptosis by disrupting MUFA-mediated protection. These approaches may mitigate resistance and enhance the therapeutic efficacy of SCD1 inhibition (22,23). More research is needed to verify whether such methods are feasible for circumventing SCD1 resistance.

A limitation of this paper is that only one cell line, A549, was used, which may not be representative of all types of lung cancer types or treatment methods. Although the inhibition of SCD1 may seem to work on this type of cells, there are many more types of lung cancer cells, such as small-cell lung carcinoma cell lines (SCLC), which are a completely different species of cells in comparison to NSCLC. Therefore, this study may overgeneralize this method's impact on lung cancer. Future studies could expand on this paper's findings by utilizing diverse cell lines to achieve a more robust conclusion on the ability of SCD1 inhibition to suppress Cancer Stem Cell growth.

In addition, another limitation of this study is that it was performed solely at the cellular level. While cellular-level experiments are useful for studying early molecular interactions and pathways, they do not reflect the full complexity and diversity of real tumor environments, as tumors consist of millions of cancer cells. Thus, this study may not fully explain the mechanism required to pursue this method in actual cancer therapeutics. Thus, further detailed mechanisms regarding how SCD1 is associated with the treatment resistance of CSCs are necessary.

Going forward, one worthwhile research direction would be taking this topic beyond the cellular level and exploring how SCD1 inhibition affects the entire tumor, such as tumor growth, suppression of spread to other parts of the body, and shifting the reactions to current treatment methods. SCD1 inhibition could be combined with existing therapies such as chemotherapy, radiation, and immunotherapy to make them more effective. Moreover, combining SCD1 inhibition with ferroptosis inducers or SFA supplementation may further enhance anti-tumor activity. In conclusion, this research paper sets the foundation for broader-scale studies, including combinatory therapies and *in vivo* modeling of CSC-targeted mediation.

## 5 Conclusion

In conclusion, this study demonstrated that SCD1 plays a crucial role in mediating the resistance of lung CSCs to ROS-induced cytotoxicity (Figure 7). Greater SCD1 expression in CSCs was found through both western blotting and PCR analysis, suggesting its importance in sustaining lung cancer cell viability and stemness. Functional inhibition of SCD1 not only sensitized CSCs to oxidative stress but also enhanced cell death when combined with ferroptosis inducers, indicating its potential as a therapeutic target. Further investigation is required to explain the underlying mechanism regarding the SCD1-mediated ROS resistance in lung CSCs.

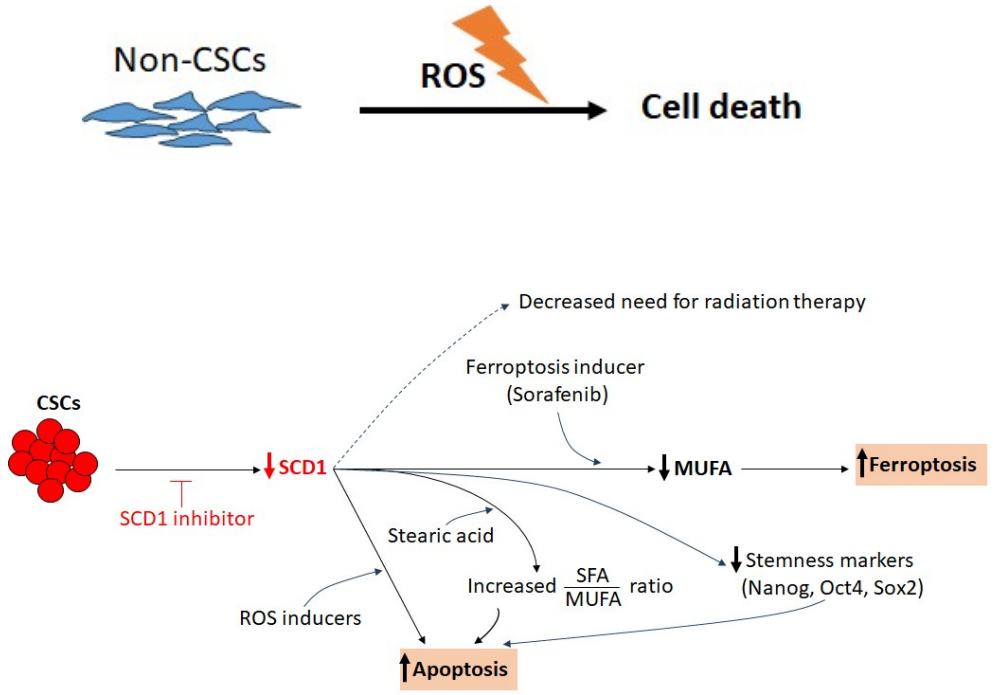


**Figure 7.** Summary of SCD1-mediated ROS resistance in lung CSCs.

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