SAT1-Mediated Spermidine Metabolism Drives Ferroptosis in Cervical Cancer

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Abstract

Background

Spermidine (SPD) dysregulation is common in multiple cancers and is associated with reduced survival of cervical cancer (CC) cells. However, the mechanisms underlying SPD's role in CC progression remain poorly understood. This study aimed to investigate how SPD metabolism influences ferroptosis in cervical cancer.

Methods

Using bioinformatics analysis of public databases and immunohistochemistry on clinical specimens, we assessed the expression of SPD metabolic enzymes. In vitro experiments were conducted using HeLa and SiHa cervical cancer cell lines. Cell viability was measured by CCK-8 assay, mitochondrial morphology was observed via transmission electron microscopy, and protein expression was analyzed by Western blot. Reactive oxygen species (ROS) and malondialdehyde (MDA) levels were quantified using fluorescent probes and biochemical assays. Statistical significance was determined using Student’s t-test or one-way ANOVA.

Results

We identified elevated expression of the rate-limiting SPD metabolic enzyme SAT1 in cervical cancer tissues. SPD treatment induced ferroptosis in CC cells, as demonstrated by decreased Glutathione Peroxidase 4 (GPX4) expression, increased ROS and MDA levels, and characteristic mitochondrial alterations. Overexpression of SAT1 or supplementation with its downstream metabolite N^1-acetylspermidine enhanced ferroptosis. Importantly, both SPD and N^1-acetylspermidine attenuated the ferroptosis resistance caused by SAT1 inhibition.

Conclusion

Our findings reveal that enhanced SAT1-mediated SPD metabolism promotes ferroptosis in cervical cancer, suggesting that targeting this metabolic pathway could represent a novel therapeutic strategy for CC treatment.

1 Introduction

cervical cancer accounts for approximately 660,000 new cases annually among women worldwide[1]. Current treatment modalities often yield suboptimal outcomes, underscoring the need for novel metabolic intervention strategies. Emerging evidence highlights the vaginal microecology as a key area

in cervical cancer research. Metabolites derived from the vaginal microbiota can traverse host barriers and influence systemic health in high-risk individuals, with disruptions in mannose, polyamine, lipid, and phenylpropionic acid metabolism pathways—largely attributable to microbial dysbiosis—implicated in cervical cancer progression[2–4].

Spermidine (SPD) is one of the important polyamines, and our previous study found that the expression level of SPD in vaginal secretions decreased significantly with the progression of cervical cancer[5]. It suggesting that SPD may influence the progression of cervical cancer. Some researchers have suggested that SPD may inhibit tumors by affecting the lipid homeostasis of tumor cells or anti-tumor immune responses, which are inseparable from its metabolism in cells[6, 7]. However, the exact mechanism is not clear. The rate-limiting enzyme in the SPD metabolic pathway, spermidine/spermine N^1-acetyltransferase (SAT1), has been shown to play a role in a variety of tumors. Expressed in the context of limiting glutamine uptake, activation of SAT1 would lead to growth inhibition in lung cancer[8]. However, its acetylation properties contribute to some extent to the resistance of gliomas to radiotherapy[9], suggesting that SAT1 has multiple roles in tumors, but, at present, no study has elucidated the role of SAT1-mediated SPD metabolism in cervical cancer.

Ferroptosis is a newly identified type of programmed cell death characterized by the iron-dependent accumulation of lipid peroxidation, which ultimately leads to oxidative damage leading to cell death[10]. Numerous disorders, including cancer, neurological diseases, organ damage, infectious diseases, etc., have been linked to the pathophysiology of dysregulation of the ferroptosis network[11]. It is noteworthy that P53 may be involved in ferroptosis in human sarcoma cells, breast cancer cells, and lung cancer cells[12]. SAT1 has been found to be a transcriptional target of the p53 protein in non-small cell lung cancer, and it plays a role in the ROS stress-mediated response to ferroptosis[13]. Even yet, it has been demonstrated that upregulating SAT1 can cause ferroptosis in adenocarcinomas in a synergistic manner, which lowers the invasion and proliferation of pancreatic cancer cells[14, 15], and offers a novel approach to tumor treatment. However, whether SAT1 plays a role in inducing ferroptosis in cervical cancer remains largely unknown. It suggests that studies targeting SAT1-mediated SPD metabolism may reveal pathways that sensitize cervical cancer to ferroptosis. Therefore, we hypothesized that the SPD-SAT1 metabolic pathway induces ferroptosis in cervical cancer.

In this work, we demonstrated through *in vitro* assays that SPD inhibits cervical cancer cell growth by inducing ferroptosis. Mechanistically, SPD reversed ferroptosis resistance resulting from SAT1 downregulation, an effect mimicked by its downstream metabolite N^1-acetylspermidine. Our results underscore the functional significance of SAT1-mediated SPD metabolism in ferroptosis induction in cervical cancer. We propose, for the first time, that SPD metabolism suppresses cervical cancer through ferroptosis promotion, expanding the scope of metabolic therapeutic strategies for this malignancy.

2 Material and Methods

2.1 Bioinformatics analysis

For tumors without normal control tissues, we analyzed gene expression in different tumor tissues by using the “Expression Analysis - Box Plot” module of the GEPIA2 (Gene Expression Analysis Interactive, Version 2) database (http://gepia2.cancer-pku.cn/#analysis) under the *P*-value cutoff = 0.01 and log2 FC (fold change) cutoff = 1, we observed the expression of SAT1, SMS, SRM genes in different tumor tissues and control tissues. Meanwhile, we obtained the box plots of SAT1 gene in cervical cancer in different pathological stages and the relationship between SAT1 and some survival outcomes of cervical cancer in the the Gene Set Cancer Analysis (GSCA: Gene Set Cancer Analysis) database database. And the protein expression levels of SAT1 in normal/ cervical cancer tissues were compared in the Human Protein Atlas (HPA, https://www.proteinatlas.org/search/SAT1) database.

We searched the Chipbase 3.0 database (https://rnasysu.com/chipbase3/network.php) to find the transcription factor sets of SAT, GPX4 and ALOX15, and searched the DAVID database (DAVID Functional Annotation) to find the transcription factor sets of SAT, Glutathione peroxidase 4(GPX4) and ALOX15. Bioinformatics Microarray Analysis) for GO and KEGG pathway analysis.

2.2 Tissue source

This study was approved by the Ethics Committee of Wuxi Maternal and Child Health Hospital (Ethics Approval No. 2025-01-0126-02). Information on 6 patients with cervical cancer (N = 6) and 6 patients with low-grade squamous intraepithelial lesions of the cervix (N = 6) attending Wuxi Maternal and Child Health Hospital between January 2025 and June 2025 was collected, and immunohistochemistry testing was performed using the remaining pathology sections after informed consent was obtained.The study subjects needed to meet the following conditions: age 18–75 years old; weight ≥ 45kg; biopsy tissues participating in cervical cancer screening were pathologically confirmed to be squamous carcinoma of the cervix (cervical cancer group) or low-grade squamous intraepithelial lesion of the uterine cervix (LSIL group); and the patients themselves were already aware of their condition. Exclusion criteria: patients receiving preoperative radiotherapy; patients suffering from serious internal diseases; patients suffering from other malignant tumors.

2.3 Immunohistochemistry (IHC) assay

Paraffin sections (5 μm thick) from 12 eligible patients were deparaffinized and rehydrated, and heat-mediated antigen retrieval was performed using tris-ethylenediaminetetraacetic acid. Endogenous peroxidase activity was blocked by adding 50 μl of 3% hydrogen peroxide solution to each section and reacting for 10 min at room temperature. The primary antibody used in this study was anti-SAT1 (abcam, ab244505, 1:40). Sections were incubated overnight at 4°C with primary antibody.

Next, slides were incubated with polymer enhancer (Reagent A) for 20 min at room temperature, and then 50 μl of anti-rabbit polymer containing peroxidase-labeled anti-rabbit polymer (Reagent B) was added to each section and reacted for 30 min at room temperature. The sections were then developed with DAB chromogen, counterstain with hematoxylin, and rinsed again with water. The films were

differentiated with 0.1% hydrochloric acid, rinsed with tap water and sealed with neutral resin. Observations were made using a microscope and evaluated by two pathologists.

IHC results were evaluated according to the intensity of staining (0 for no staining, 1 for light yellow, 2 for tan, and 3 for brown) and the percentage of positive cells (1 for 0–25%, 2 for 25–50%, 3 for 50–75%, and 4 for 75–100%). The two scores were then multiplied to give the protein expression value.

2.4 Cell culture

Human cervical cancer cell lines HeLa, Siha were purchased from the Cell Resource Center, Shanghai Institutes for Life Sciences, Chinese Academy of Sciences. Hela was incubated in 1640 (Hyclone, USA) with 10% FBS and Siha was incubated in DMEM (Hyclone, USA) with 10% FBS. Cells were cultured at 37℃ and 5% CO2.

2.5 Cell viability analysis

Hela cells (5×10^3 cells/well) were seeded in a 96-well plate. Cells were were treated with different concentrations of SPD (Aladdin, S107071, China)(0, 25, 50, 100, 200 μM) for 24h after adhesion, while blank control wells were set up.Then, 10μL of CCK-8 solution (APO & BIO, USA) was added to each well for further incubation for 2 h at 37℃. The absorbance at 450 nm was tested by an enzyme meter.

2.6 Reactive oxygen species (ROS) assay

Intracellular ROS levels were measured using the fluorescent probe DCFH-DA (Abbkine, KTB1910, China). Hela, Siha cells were inoculated in 24-well plates overnight. Then the cells were treated with SPD, SAT1 inhibitor Berneil (Aladdin, D129481, China), SAT1 activator Denspm (Aladdin, N287060, China CHINA), N^1-Acetylspermidine hydrochloride (Aladdin, N588802, China) for 6-10h. After removing the drugs, the cells were incubated with the kit solution at a 10 mM for 90 min in the dark according to the instructions. Cells were rinsed with PBS 3 times before images were acquired using a fluorescence microscope (Leica, Germany). Finally, intracellular ROS levels were quantified using Image J software.

2.7 Malondialdehyde (MDA) assay

MDA levels in Hela, Siha cells were measured by the Lipid Peroxidation MDA Assay Kit (Abbkine, ktb1050, China) with the provided instructions.. About 5×10^6 cells were harvested and the extraction buffer was added to mix. Cells were lysed by ultrasonic cell pulverizer, and the supernatant was collected after low temperature centrifugation. The supernatant:reaction solution = 1:3 was added to a 1.5 ml centrifuge tube, mixed thoroughly and incubated at 95°C in a metal bath for 30 min, centrifuged at low temperature and the supernatant was aspirated to a 96-well plate. Each sample was identified by enzyme markers at appropriate wavelengths (532 nm, 600 nm).The level of MDA was standardized by the amount of proteins in the cell lysate.

2.8 Western blotting

Total protein was extracted from the cells by RIPA buffer (Beyotime, China). Protein estimation was performed using BCA kit (Beyotime, China). Proteins were separated by gel electrophoresis and transferred to PVDF membrane. After sealing with 5% skimmed milk, the blot was probed with primary antibody at 4°Covernight. Subsequently, the blot was incubated with secondary antibody (Cwbio, China). Signals were visualized by ECL kit (Beyotime, China). Primary antibodies used in Western blotting: SAT1 (Protein Tech, 10708-1-AP, 1:500), TFRC (Protein Tech, 10084-2-AP, 1:5000), GPX4 (Boster, BM5231, 1:2000) and anti-β-actin (Boster, BM0627, 1: 4000).

2.9 Transmission electron microscopy

A number of 10^7 Hela cells were collected and immediately fixed in 2.5% glutaraldehyde fixative for 4 h. The cells were rinsed 3 times with 0.1 M phosphate buffer PBS (PH 7.0). The fixed specimens were then dehydrated in acetone. Thereafter, transition was made to 90% and 95% acetone solutions for 15 min each. finally, the specimens were treated twice with pure acetone for 20 min each. samples were permeabilized with acetone and then polymerized and encapsulated by oven polymerization at 60°Cfor 48 h. Ultra-thin sections of 70–90 nm were sliced using an ultrathin slicer (Leica, Switzerland). After staining with uranyl acetate and lead citrate together, the sections were photographed and observed under a transmission electron microscopy (Hitachi, Japan), and the images were collected and analyzed.

2.10 Statistical analysis

GraphPad Prism 9.5 software was used for statistical analysis level graphing. Data were expressed as the mean of three individual replicates ± standard deviation (SD). Data were analyzed by Student t-test or one-way ANOVA. $P < 0.05$ was considered significant.

3 Result

3.1 SPD induces ferroptosis in cervical cancer cells

SPD has been shown to effectively kill tumor cells in breast cancer[16], hepatocellular carcinoma[17] and neuroblastoma[18] through apoptosis, autophagy, and other means. To further understand the effect of SPD on cervical cancer Hela cells, we first assessed the effect of various SPD concentrations on cell viability. the results of the CCK-8 experiment revealed that the cell viability of Hela reduced dramatically as SPD concentration increased, but Ferrostatin-1 (Fer-1), an ferroptosis inhibitor, rescued the process (Fig. 1A). Subsequently, We used transmission electron microscopy to see how the mitochondrial morphology of the SPD-treated Hela cells changed, including increased membrane density, membrane rupture, and decreased mitochondrial cristae(Fig. 1B).

This suggests that SPD has the ability to cause ferroptosis in cervical cancer cells. GPX4 regulates cellular iron metabolism and redox balance[19]. It is one of the key antioxidant enzymes, and its deletion or dysfunction will lead to the accumulation of intracellular peroxides, resulting in the occurrence of ferroptosis[20, 21]. Thus, we used a Western blot to investigate SPD's impact on GPX4. As SPD therapy

was prolonged, it was discovered that the amount of the GPX4 protein gradually dropped (Fig. 1C-D). Furthermore, Hela cells showed a substantial upregulation of ROS and MDA (Fig. 1E-F). Together, these results imply that SPD causes ferroptosis in cervical cancer cells, potentially through interference with the antioxidant mechanism regulated by GPX4.

3.2 SPD metabolism rate-limiting enzyme SAT1 is highly expressed in cervical cancer

Using the GEPIA2 database, we first assessed the expression levels of important spermine metabolism enzymes in 306 cervical cancer tissues and 13 adjacent normal tissues to evaluate the metabolic process of spermine in cervical cancer cells. (Fig. 2A). The findings demonstrated that the levels of spermidine metabolizing enzymes were all significantly elevated in cervical cancer patients particularly SAT1, compared with controls (Fig. 2B-D). To explore the protein expression levels of SAT1 in cervical cancer tissues, we utilized the HPA database, as well as pathology sections from patients with cervical cancer and LSIL for analysis. IHC showed that SAT1 was expressed in the nucleus and cytoplasm of the cells, with higher levels of expression in cervical cancer relative to controls (Fig. 2E-F).

3.3 SAT1 overexpression exacerbates ferroptosis in cervical cancer

In the above studies, SAT1 is considered to be one of the key transcription factors affecting ferroptosis[22, 23]. However, due to the complexity of the tumor microenvironment, the way in which SAT1 affects ferroptosis in tumors is highly conflicting. In order to better understand the precise function of SAT1 in causing ferroptosis in cervical cancer, we treated Hela and Siha cells with the SAT1 activator DENspm (10 mM) and evaluated the effects of activation on indicators linked to ferroptosis using western blot. In HeLa cells, it was discovered that DENspm could considerably increase the expression level of SAT1 and decrease GPX4 more than cells treated with SPD alone (Fig. 3A-C).The same phenomenon was also observed in Siha cells (Fig. 3E-G). We then used MDA kits to measure the amounts of MDA in the two cell types independently (Fig. 3D, H). In the absence of SPD or DENspm activation, HeLa and SiHa cells displayed negligible levels of MDA and ROS. MDA levels in Hela cells increased two to three times when SAT1 was activated. According to the findings of ROS detection (Fig. 3I), ROS in Hela cells in particular may increase by 6–7 times. These findings imply that the induction of ferroptosis levels in cervical cancer may be made worse by SAT1 activation.

3.4 SAT1 may influence metal ion binding

3.5 SAT1 mediates the function of SPD-induced ferroptosis.

To study the functional involvement of SAT1 in causing ferroptosis in cervical cancer, Hela and Shia cells were treated with the SAT1-specific inhibitor Berenil alone or in conjunction with SPD. After 6 hours of treatment with 10 μM Berenil, GPX4 protein expression rose by 1.4-fold in both HeLa and SiHa cells.

Following treatment with 10 μM Berenil, GPX4 protein expression rose 1.4-fold in both HeLa and SiHa cells. However, when combined with SPD, GPX4 expression in cervical cancer cells was recovered by around 30.6% in both cases.(Fig. 5A-B)

Combined with the above bioinformatic analysis results. When used western blot to identify GPX4, we concurrently evaluated TFRC expression. Parallel to SAT1 inhibition, TFRC protein levels were observed to be decreased by 26% and 29.7% in HeLa and SiHa cells, respectively. TFRC was restored by 43% and 83.9% with the addition of SPD (Fig. 5A-B).

In addition, we discovered that ROS (Fig. 5C-D), MDA (Fig. 5E, G) and Fe^{2+} (Fig. 5F, H)of both cell lines followed the same trend as TRFC. Notably, Hela cells seemed to be more susceptible to oxidative stress. These findings indicate that down-regulation of SAT1 initiates ferroptosis resistance in cervical cancer cells; however, the addition of SPD was able to restore the ferroptosis level of cervical cancer cells to some extent, implying that SPD-induced ferroptosis in cervical cancer cells requires the mediation of SAT1.

3.6 Acetylation product rescues ferroptosis resistance induced by SAT1 downregulation

The rate-limiting enzyme in the SPD acetylation metabolic pathway, SAT1, converts SPD to N^1-Acetylspermidine. To assess the influence of N1-Acetylspermidine on the induction of ferroptosis in cervical cancer cells, we blocked SAT1 and subsequently introduced N^1-Acetylspermidine, observing whether the degree of ferroptosis altered at this time.

Similar to prior investigations, we discovered via western blot that down-regulating SAT1 levels reduced the total level of ferroptosis. The expression of GPX4 in cervical cancer cells was dramatically raised, and the expression of GPX4 in Hela and Siha was rescued by 33.6% and 36.8% when Berenil was combined with N^1-acetylspermidine, respectively, compared to Berenil alone. TFRC followed the same pattern when SAT1 was blocked (Fig. 6A-B). However, the following administration of N^1-acetylspermidine increased TFRC expression.

Next, we investigated the levels of ROS, MDA and Fe^{2+} in the cells. The addition of N^1-acetylspermidine resulted in a more rapid and intense oxidative stress response in the cells. N^1-acetylspermidine treatment increased ROS in Hela cells by 6.8-fold compared to untreated cells (Fig. 6. K), which was approximately 1.44-fold greater than SPD alone (Fig. 6C-D). Consistent with this, MDA accumulation in Hela cells was 2.8-fold higher than in untreated cells, 1.8-fold higher than when SPD was applied alone, and Berenil was restored to lower MDA levels (Fig. 6E, G). The change in Fe^{2+} showed the same trend as MDA (Fig. 6F, H)

However, Siha cells did not produce the same effect. Finally, we conclude that N^1-Acetylspermidine recovered the ferroptosis resistance caused by SAT1 down-regulation while aggravating the severity of

the reaction.

4 Discussion

SPD suppresses tumor growth in a number of methods, some of which are closely linked to its metabolic fate. Nevertheless, much remains unknown about the exact function of SPD metabolism in cervical cancer. In this study, we initially confirmed the growth inhibitory effect of SPD on cervical cancer cells through in vitro assays. Co-treatment with the ferroptosis inhibitor Fer-1 partially rescued cell viability, suggesting the involvement of ferroptosis in SPD-induced cell death. Consistent with this, transmission electron microscopy revealed mitochondrial alterations characteristic of ferroptosis, including increased membrane density, membrane rupture, and reduced cristae. Further supporting this, we observed a time-dependent decrease in GPX4 protein expression following SPD treatment, accompanied by elevated levels of ROS and MDA.

Bioinformatic analysis revealed that key enzymes involved in SPD metabolism, particularly the rate-limiting enzyme SAT1, were significantly upregulated in cervical cancer tissues compared to controls SAT1 may influence disease progression in patients with cervical cancer, especially in advanced stages, emphasizing the possibility of modulating SAT1-mediated SPD metabolism for cervical cancer treatment.

Ferroptosis is a regulated cell death process driven by lipid peroxidation and intricate metabolic interactions. Acetylation modifications have emerged as important regulators of ferroptosis in cancer [24–26]. For instance, acetylation of p53, ALOX12, and HSPA5 has been shown to promote ferroptosis in various tumor contexts[26–28]. Our findings suggest that SAT1-mediated acetylation of SPD may similarly influence ferroptosis susceptibility in cervical cancer. This is supported by previous studies in lung and pancreatic cancers, where SAT1 overexpression enhanced ferroptosis and suppressed tumor growth[14, 29]. In our study, both SPD and its acetylated metabolite *N*¹-acetylspermidine reversed the ferroptosis resistance conferred by SAT1 inhibition, reinforcing the notion that SAT1-dependent SPD metabolism drives ferroptosis in cervical cancer cells.

Through transcription factor network analysis, we identified 23 overlapping transcription factors among SAT1, GPX4, and ALOX15, including SP1 and KLF4, which are associated with oxidative stress responses. These factors may represent promising targets for future therapeutic interventions.

Notably, we observed differential sensitivity to SPD- and SAT1-mediated ferroptosis between the two cervical cancer cell lines, HeLa and SiHa. While both cell lines showed consistent trends in GPX4 suppression and TFRC/Fe^{2+} accumulation upon SAT1 activation, the magnitude of the response, particularly in ROS and MDA production, varied. HeLa cells exhibited a more pronounced ferroptotic response compared to SiHa cells. However, compared with other tumor cells, such as colorectal cancer cells, the iron ion content in cervical cancer cells was at a lower level, and the content in HeLa cells was lower than that in Siha[30–32]. This divergence may be attributed to intrinsic differences in their

antioxidant capacity, iron metabolism, or other cell line-specific metabolic backgrounds, given that HeLa and SiHa represent adenocarcinoma and squamous carcinoma subtypes, respectively. Future studies are warranted to delineate the precise molecular determinants underlying this differential susceptibility.

In summary, we demonstrate that downregulation of SAT1 expression reduces ferroptosis levels in cervical cancer cells, whereas SPD or N^1-acetylspermidine restores ferroptotic cell death. These results underscore the importance of the SAT1-mediated SPD acetylation pathway in promoting ferroptosis and suggest that monitoring SPD/SAT1 levels or pharmacologically activating this pathway could offer novel avenues for cervical cancer treatment.

Abbreviations

SPD
Spermidine
ROS
Reactive oxygen species
MDA
malondialdehyde
GPX4
Glutathione Peroxidase 4
SAT1
spermidine/spermine N1-acetyltransferase
LSIL
low-grade squamous intraepithelial lesion of the uterine cervix
TFRC
transferrin receptor

Declarations

Authors' contributions

XR. PENG and Z.J. wrote the main manuscript text and WQ. YUAN prepared Figs. YX.YIN and JQ. ZHANG. analyzed data in Figs. MD. LU and DZ.CHEN supervised this project.

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Data availability

The datasets supporting the conclusions of this study are available in the GEPIA2 (Gene Expression Analysis Interactive, Version 2) database, the Gene Set Cancer Analysis (GSCA: Gene Set Cancer Analysis) database database and the Human Protein Atlas (HPA , https://www.proteinatlas.org/search/SAT1) database.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Wuxi Maternal and Child Health Hospital (Ethics Approval No. 2025-01-0126-02).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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