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Original Article

SCARA5 might be one potential marker for CC and promoted Ferroptosis by FTL

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Abstract: The current investigation sought to explore the effects and its possible mechanisms of Scavenger receptor class A member 5 (SCARA5) in model of colon cancer (CC). Patients diagnosed with CC were recruited from our hospital. SCARA5 mRNA expression levels in patients with CC was reduced, and the expression of SCARA5 mRNA in patients with I-II was higher than that of patients with III-IV. The overall survival (OS) and disease-free survival (DFS) of SCARA5 high expression were higher those of SCARA5 low expression in patients with CC. Sh-SCARA5 promoted CC in mice model. SCARA5 up-regulation reduced cell growth of CC. SCARA5 up-regulation promoted Ferroptosis of CC by the inhibition of mitochondrial damage. SCARA5 up-regulation induced ferritin light chain (FTL) protein expression. Si-FTL attenuated the effects of SCARA5 on Ferroptosis in CC. The SCARA5 protein interlinked with the FTL protein. SCARA5 up-regulation reduced FTL protein ubiquitination. Up-regulation of SCARA5 suppressed cell growth in CC. SCARA5 up-regulation enhanced ferroptosis in CC by inhibiting mitochondrial damage. We conclude that SCARA5 promoted ferroptosis in CC cells by inhibiting FTL ubiquitination-induced mitochondrial damage, which may contribute to the treatment of CC.

Keywords: SCARA5, FTL, CC, ferroptosis, ubiquitination

Introduction

Colorectal cancer is rising year by year, which seriously threatens human life and health. Radiotherapy, chemotherapy, and targeted drug therapy have become routine adjuvant treatments for advanced colorectal cancer (CRC) and recurrent cases, and have achieved certain results [1]. In China, it constitutes the most prevalent malignant tumor of the digestive tract, with colon cancer (CC) accounting for about 40% [2]. Clinically, colorectal surgeons frequently encounter resectable CC. Over the past few decades, the comprehensive treatment paradigm encompassing radical surgery combined with postoperative adjuvant chemotherapy has increased the survival rate of patients with resectable CC by about 20% [3]. The treatment effect of advanced CC patients is often not ideal, especially for elderly patients, whose cure rate is relatively lower and the mortality rate is higher [3]. Late stage CC patients who have received three different treatment options are called third line treatment patients. These patients face the challenge of not having effective treatment drugs to choose from, which is a clinical treatment problem [4]. Consequently, the efficacy of existing adjuvant chemotherapy strategies has yet to attain an exceedingly satisfactory level, thereby necessitating continuous optimization [5].

CC has the characteristics of easy metastasis, easy recurrence, and easy drug resistance. Tumor cells have an increased demand for iron, making them more prone to iron overload and iron death [6]. Ferroptosis, has been continuously attracting attention in tumor research and has emerged as a research hotspot [7]. Especially when alpha fetoprotein levels are low, ferritin can be combined to increase the efficiency of liver cancer diagnosis [8]. Compared to normal tissues, many tumor tissues have higher levels of ferritin [9, 10]. Particularly when the level of alpha fetoprotein is low, ferritin can be combined to enhance the efficiency

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of liver cancer diagnosis [11]. In contrast to normal tissues, numerous tumor tissues exhibit higher levels of ferritin [12].

Scavenger receptor class A member 5 (SCARA5) remains functionally undefined despite its bodily defense role and chromosomal location at 8p21.1. Comprising 495 amino acids, the gene spans a total length of 3.644 kb [13]. In recent years, research has found a close relationship between the SCARA family and malignant tumors. For example, studies have found that the SCARA3 gene is downregulated in prostate cancer due to promoter methylation and is associated with tumor metastasis. Exogenous expression of SCARA3 can significantly reduce the clonogenic ability and anchor independent growth of prostate cancer cell lines [14]. Specifically, hypermethylation and allelic imbalance in the SCARA5 promoter region contribute to its low expression in liver cancer cells [15, 16]. The current investigation sought to explore the effects and its possible mechanisms of SCARA5 in model of CC.

Materials and methods

Patients

A total of patients with cervical cancer were obtained at The Ethics Committee of Daqing Oilfield General Hospital from January 2018 to May 2019 (2021-091). The written informed consents were obtained from all the subjects and this study was approved by the Ethics Committee of our hospital.

Quantitative PCR

qRT-PCR assays were performed using LightCycler® 480 real-time PCR system. The mRNA expression levels were normalized to the GAPDH expression using the $2^{-\Delta\Delta ct}$ method.

Cell culture and RNA interference

Colon carcinoma cell lines (SW620, HCT116, LOVO, SW480 cells) and colon normal cell line (HCoEpiC cells) were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum in a humidified atmosphere of 5% CO_2 at 37°C. Si-SCARA5 plasmids were transfected into SW620 cells, or SCARA5 plasmids were transfected into SW480 cells using Lipofectamine 2000.

Western blot analysis and immunofluorescence

The membrane was incubated with anti-SCARA5 antibody (1:1000, ab118894, abcam); anti-FTL antibody (1:1000, 3998, Cell Signaling Technology, Inc.), anti-GPX4 antibody (1:1000, ab12506, abcam) and anti-β-actin antibody (1:5000, GB15003-100, servicebio) at 4°C overnight. Then first antibodies were removed and TBST wash membrane using TBST. Membranes were incubated with the secondary antibody at room temperature.

Cells were treated with primary antibodies at 4°C overnight: anti-SCARA5 antibody (1:100, ab118894, abcam) and anti-FTL (1:100, sc-390558, abcam). Cells were then incubated with Cy3-conjugated goat anti-rabbit or goat anti-mouse IgG DyLight 488 - conjugated secondary antibodies, and stained with DAPI. Cells were observed under a fluorescent illumination microscope (Olympus IX71, Tokyo, Japan).

Proliferation assay and Ethynyl deoxyuridine (EdU) staining

After culturing at indicated time, the cellular proliferation was detected using Cell Counting Kit-8 (CCK-8) according to manufacturer's instructions.

EdU (10 mM) was added to each well and cells were fixed with 4% formaldehyde for 30 min. After washing, EdU was detected with Click-iTR EdU Kit and images were visualized using fluorescent microscope (Olympus).

Animal model

The present study was approved by The Ethics Committee of Daqing Oilfield General Hospital (No: 20210923005). All mice were induced into CC mice model using AOM + DSS according to references [16-19]. All mice were injected with control or sh-SCARA5 virus (1×10^9 PFU/mL). After 9 weeks, mice were anesthetized using 50 mg/kg of pentobarbital sodium, and sacrificed using cervical dislocation. Then, tumor were measured.

Statistical analysis

All values are expressed as means ± SEM unless specified. $P<0.05$ was considered sta-

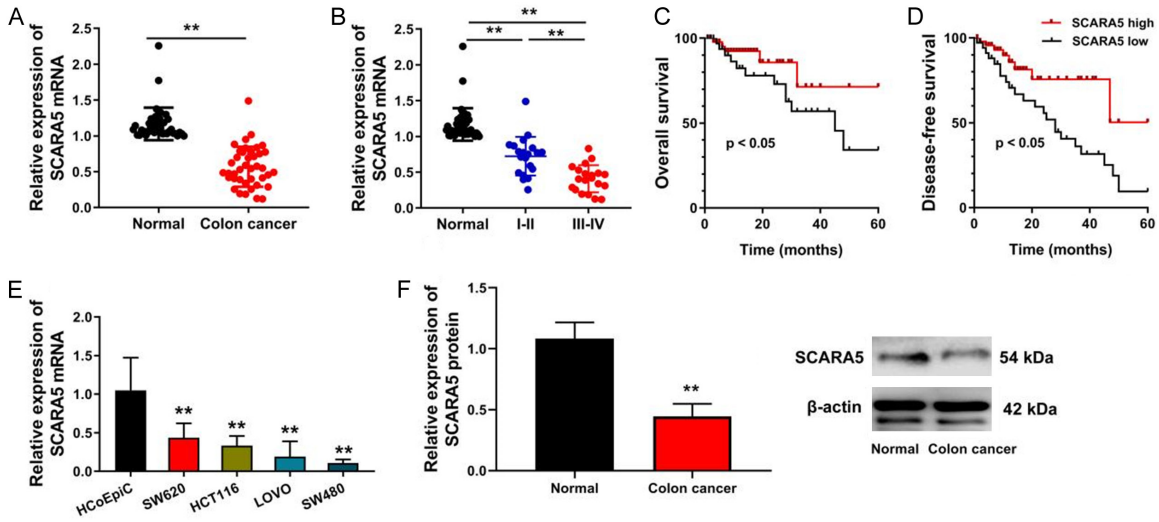


Figure 1. SCARA5 levels in model of colon cancer. SCARA5 mRNA expression (A and B), OS and DFS (C and D), SCARA5 mRNA expression in colon carcinoma cell lines (E), SCARA5 protein expression (F). OS, Overall Survival; DFS, Disease-Free Survival; **P<0.01 compared with normal or HCoEpiC.

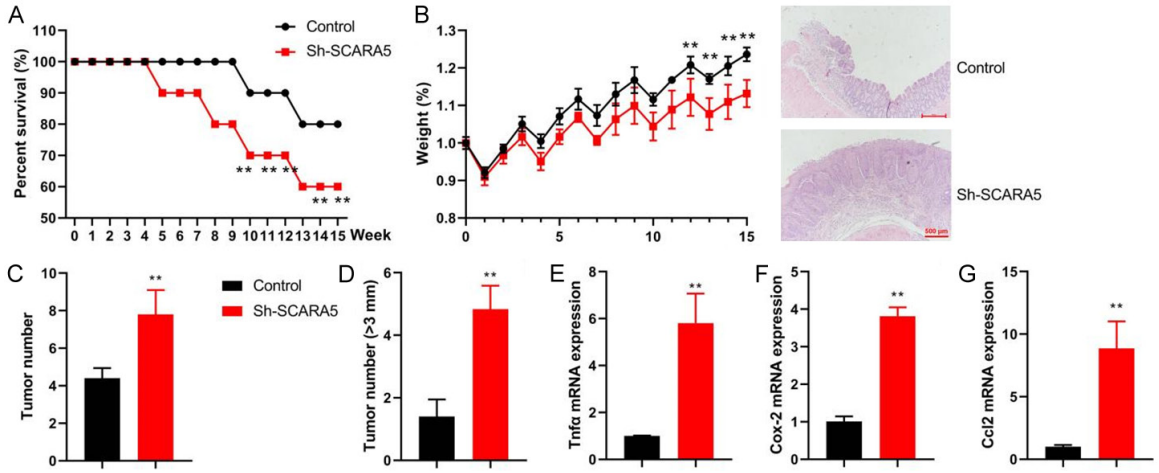


Figure 2. Sh-SCARA5 promoted colon cancer in mice model. Percent survival (A), weight (B, scale bar = 500 μm), number of colon cancer (C and D), TNF-α/COX-2/Ccl2 mRNA expression (E-G). **P<0.01 compared with Control.

tistically significant using Graphad Prism 6. The differences between groups were analysed using Student's *t*-test.

Results

SCARA5 levels in CC model

Firstly, the study ascertained that the alterations in SCARA5 in the CC model. The expression levels of SCARA5 mRNA in patients with CC were diminished, and the expression of SCARA5 mRNA in patients with stages I-II was higher than that in patients with stages III-IV (**Figure 1A**, **1B**). The OS and disease-free survival (DFS) of SCARA5 high expression were higher those of SCARA5 low expression in patients with CC (**Figure 1C**, **1D**). Then, SCARA5 mRNA expression in colon carcinoma cell lines were reduced (**Figure 1E**). Meanwhile, SCARA5 protein expression of colon tissue in patients (**Figure 1F**).

Sh-SCARA5 promotes CC in mice model

The study discerned that the effects of the SCARA5 gene in the CC model. In the mice model of CC, the sh-SCARA5 virus decreased

the percent survival and weight, promoted the volume and number of CC, and augmented TNF-α, COX-2 and Ccl2 mRNA expression levels in the mice model of CC (**Figure 2**).

SCARA5 up-regulation inhibits cell growth of CC

Furthermore, we explored whether the function of SCARA5 on cell growth of CC. The SCARA5 plasmid augmented SCARA5 mRNA expression, reduced cell growth and EDU cells, and impeded cell metastasis of CC (**Figure 3A-D**). The si-SCARA5 plasmid attenuated SCARA5 mRNA expression, enhanced cell growth and EDU cells, and promoted cell metastasis of CC (**Figure 3E-H**).

SCARA5 up-regulation promotes Ferroptosis in CC through the induction of mitochondrial damage

The study delineated that the effects of SCARA5 on Ferroptosis in CC. The upregulation of SCARA5 augmented LDH activity level and PI cells, escalated iron content, and repressed GSH activity level and GPX4 protein expression in CC cells (**Figure 4A-E**). Simultaneously, the downregulation of SCARA5 elevated LDH activity level and PI cells, enhanced iron content, and hindered GSH activity level and GPX4 protein expression in CC cells (**Figure 4A-E**). Subsequently, the sh-SCARA5 virus augmented GSH activity level and GPX4 protein expression in the mice model of CC (**Figure 4F**, **4G**). SCARA5 up-regulation curtailed JC-1 levels and MPT, and exacerbated mitochondrial damage in CC cells (**Figure 4H-J**).

Upregulation of SCARA5 triggers FTL protein expression

In addition, we probed the underlying mechanism of SCARA5 in ferroptosis of CC. SCARA5 up-regulation elicited FTL mRNA expression, and SCARA5 down-regulation induced FTL mRNA expression in CC cells (**Figure 5A**). Moreover, SCARA5 up-regulation augmented SCARA5 and FTL protein expressions and SCARA5 down-regulation dampened SCARA5 and FTL protein expressions in CC cells (**Figure 5B**, **5C**). In the mice model, sh-SCARA5 virus suppressed FTL protein expression in mice model of CC (**Figure 5D**). Confocal microscope revealed that SCARA5 up-regulation enhanced FTL expression in CC cells (**Figure 5E**).

Silencing of FTL mitigates the effects of SCARA5 on Ferroptosis in CC

The study divulged that the effects of SCARA5 on Ferroptosis in CC are mediated by FTL. Si-FTL attenuated FTL protein expression and LDH activity levels, while enhancing GPX4 protein expression and GSH activity levels in CC by SCARA5 up-regulation (**Figure 6A-C**). FTL up-regulation suppressed GPX4 protein expression and GSH activity levels, and induced FTL protein expression and LDH activity levels in CC by SCARA5 down-regulation (**Figure 6D-F**). Si-FTL diminished PI cells and iron content, and increased JC-1 levels and MPT in CC by SCARA5 up-regulation (**Figure 6G-J**). Conversely, up-regulation of FTL increased PI cells and iron content, and reduced JC-1 levels and MPT in CC by SCARA5 up-regulation (**Figure 6K-N**).

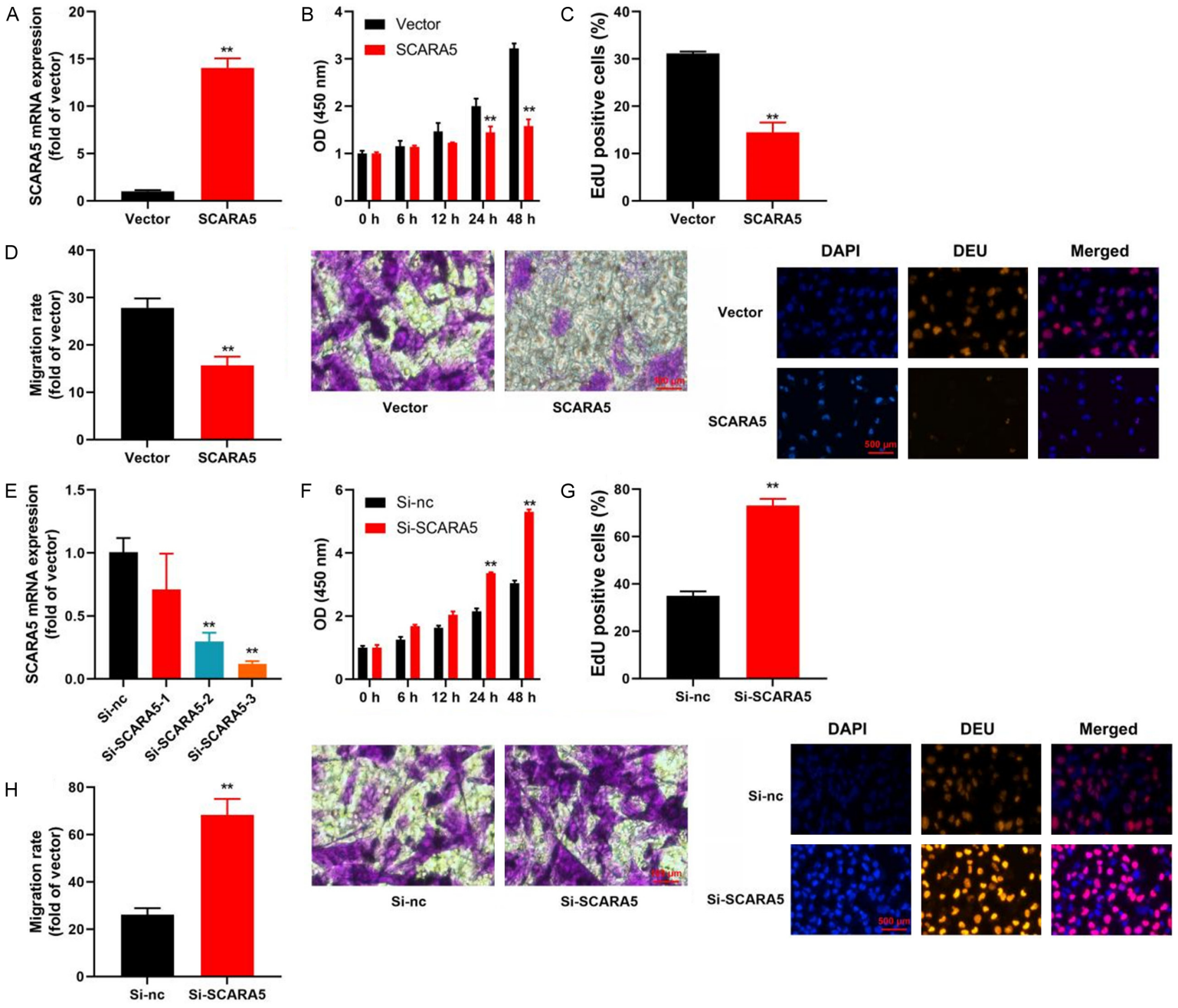
Subsequently, si-FTL abrogated cell growth and EDU cells, and impeded cell metastasis of CC cells upon SCARA5 up-regulation (**Figure 7A-C**). Conversely, up-regulation of FTL facilitated cell growth and EDU cells, and potentiated cell metastasis of CC cells upon SCARA5 down-regulation (**Figure 7D-F**).

Ferroptosis as a contributor to the effect of SCARA5 on CC

Building upon the aforementioned results, the study sought to ascertain whether Ferroptosis constitutes one of the factors influencing the effect of SCARA5 on CC. The Ferroptosis inhibitor (5 μM of YL-939) augmented cell growth and GSH activity level, and while diminishing LDH activity level, PI cells and iron content in CC cells through SCARA5 up-regulation (**Figure 8A-E**). Conversely, the Ferroptosis inducer (5 μM of FIN56) attenuated cell growth and GSH activity level, and promoted LDH activity level, PI cells and iron content in CC cells via SCARA5 up-regulation (**Figure 8F-J**).

SCARA5 protein interconnects with FTL protein

The study further characterized the mechanism of SCARA5 on ferroptosis of CC through FTL. In this study, protein structures were eliminated eliminate crystal water, small molecules, and other impurities. The proteins FTL and SCARA5 were docked using Hdock (**Figure 9A**). SCARA5 protein interlinks with WT of FTL protein, and SCARA5 protein incomplete link to FTL protein (**Figure 9B**). Likewise, FTL protein interlinked with WT of SCARA5 protein, and FTL protein


A
SCARA5 mRNA expression (fold of vector)
Vector
SCARA5
B
Vector
SCARA5
OD (450 nm)
0 h
6 h
12 h
24 h
48 h
C
EdU positive cells (%)
Vector
SCARA5
D
Migration rate (fold of vector)
Vector
SCARA5
Vector
SCARA5
DAPI
DEU
Merged
Vector
SCARA5
500 μm
E
SCARA5 mRNA expression (fold of vector)
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Migration rate (fold of vector)
Si-nc
Si-SCARA5
Si-nc
Si-SCARA5
DAPI
DEU
Merged
Si-nc
Si-SCARA5
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Figure 3. SCARA5 up-regulation reduced cell growth of colon cancer. SCARA5 mRNA expression (A and E); Cell growth (CCK-8, B and F, scale bar = 500 μm); EDU assay (C and G, scale bar = 100 μm), migration rate (D and H) in vitro model of colon cancer. **P<0.01 compared with negative group or si-negative group.

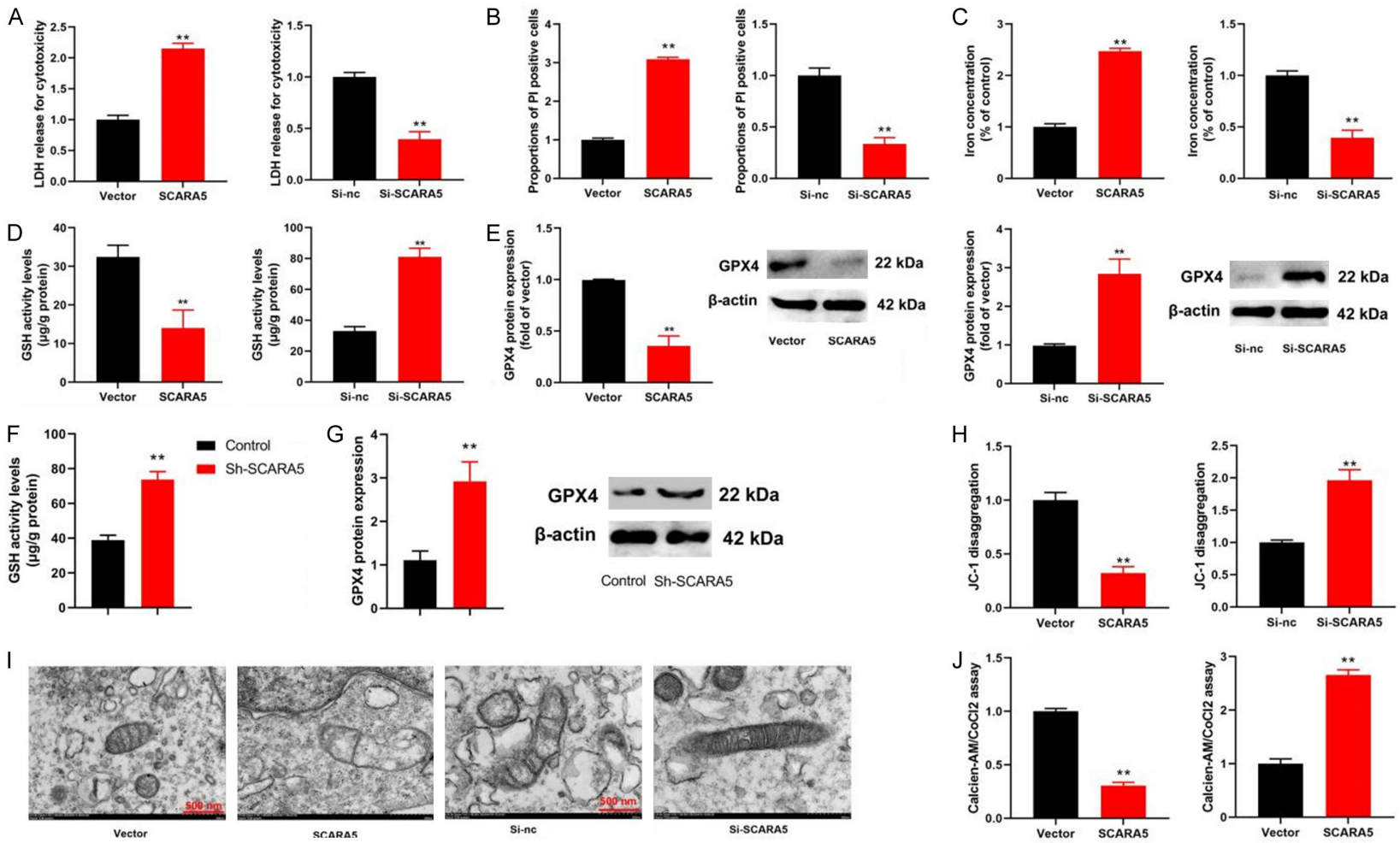

Figure 4. SCARA5 up-regulation promoted Ferroptosis of colon cancer by the induction of mitochondrial damage. LDH activity levels (A), PI cell (B), iron content (C), GSH activity levels (D), GPX4 protein expression (E), JC-1 levels (H), mitochondrial damage (electron microscope, I, scale bar = 500 nm), MPT (J) in vitro model; GSH activity levels (F and G) in mice model. **P<0.01 compared with negative group or si-negative group.

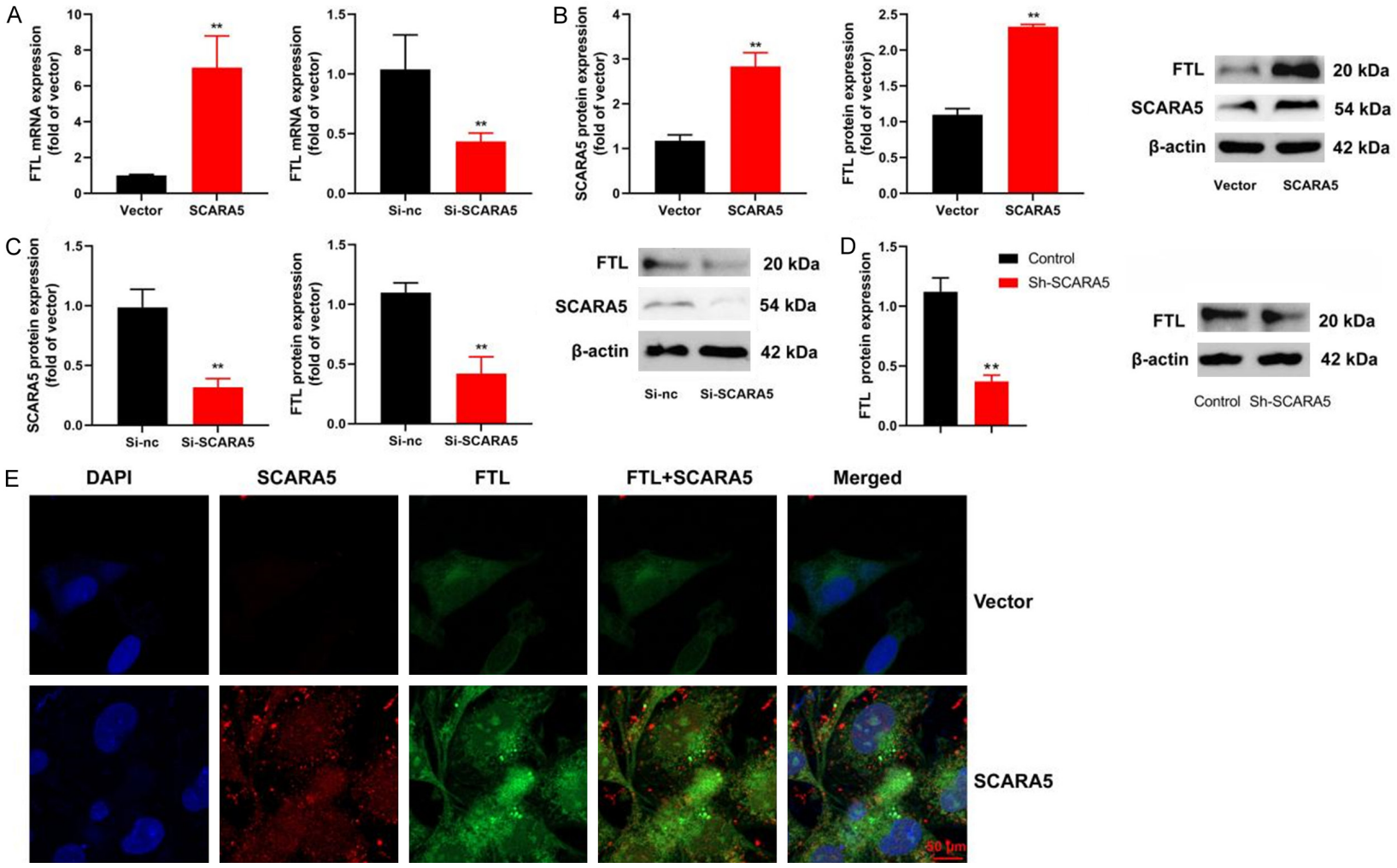

Figure 5. SCARA5 up-regulation induced FTL protein expression. FTL mRNA expression (A), SCARA5 and FTL protein expression (B and C), FTL protein expression (D), SCARA5 and FTL expression (confocal, E, scale bar = 50 μm). **P<0.01 compared with control, negative group or si-negative group.

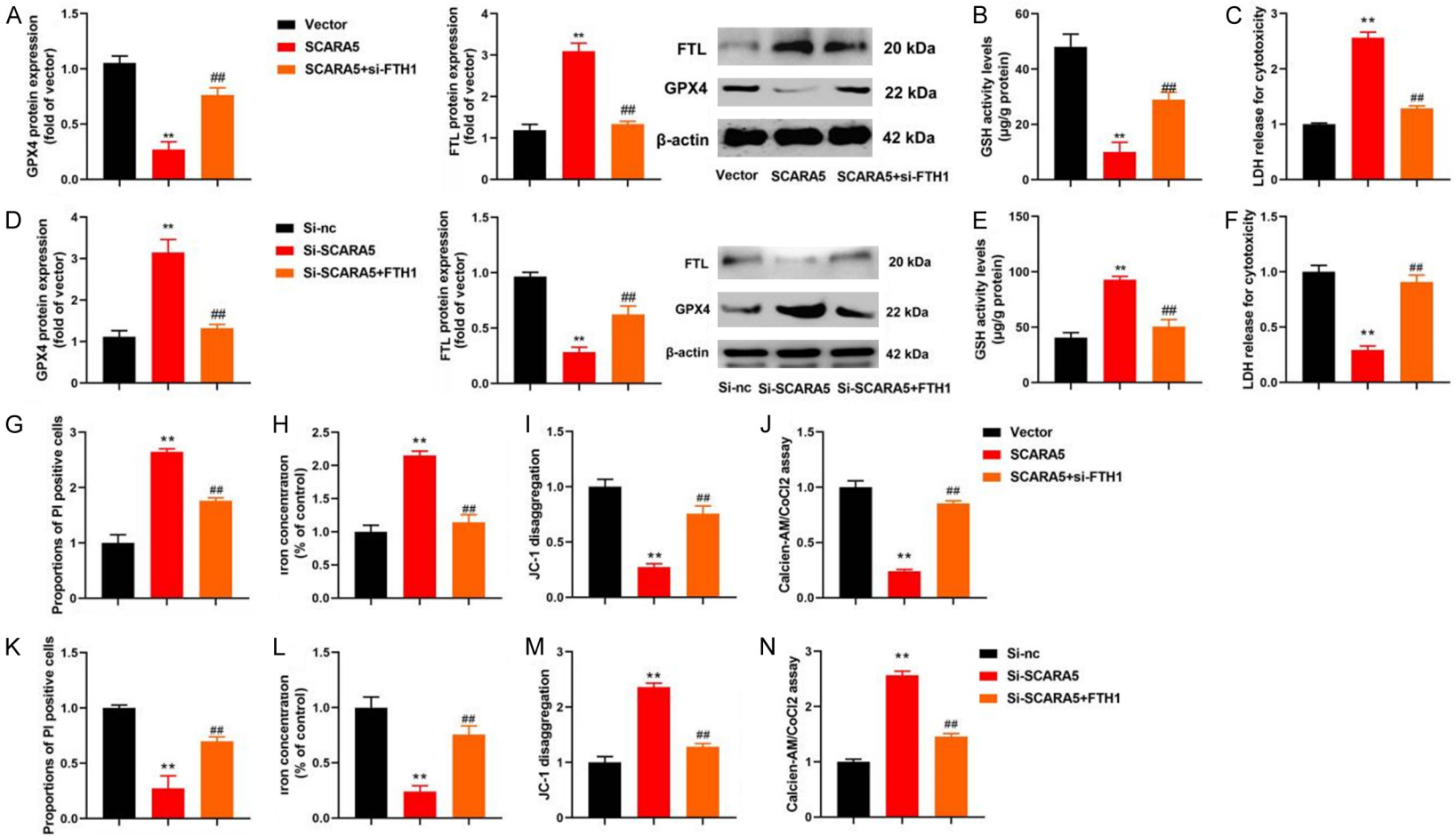

Figure 6. Si-FTL reduced the effects of SCARA5 on Ferroptosis of colon cancer. GPX4 and FTL protein expression (A), GSH activity levels (B), LDH activity levels (C), PI cells (G), iron content (H), JC-1 levels (I) and MPT (J) in vitro model by SCARA5 up-regulation and si-FTL; GPX4 and FTL protein expression (D), GSH activity levels (E), LDH activity levels (F), PI cells (K), iron content (L), JC-1 levels (M) and MPT (N) in vitro model by SCARA5 down-regulation and FTL. **P<0.01 compared with negative group or si-negative group; ##P<0.01 compared with SCARA5 up-regulation group or SCARA5 down-regulation group.

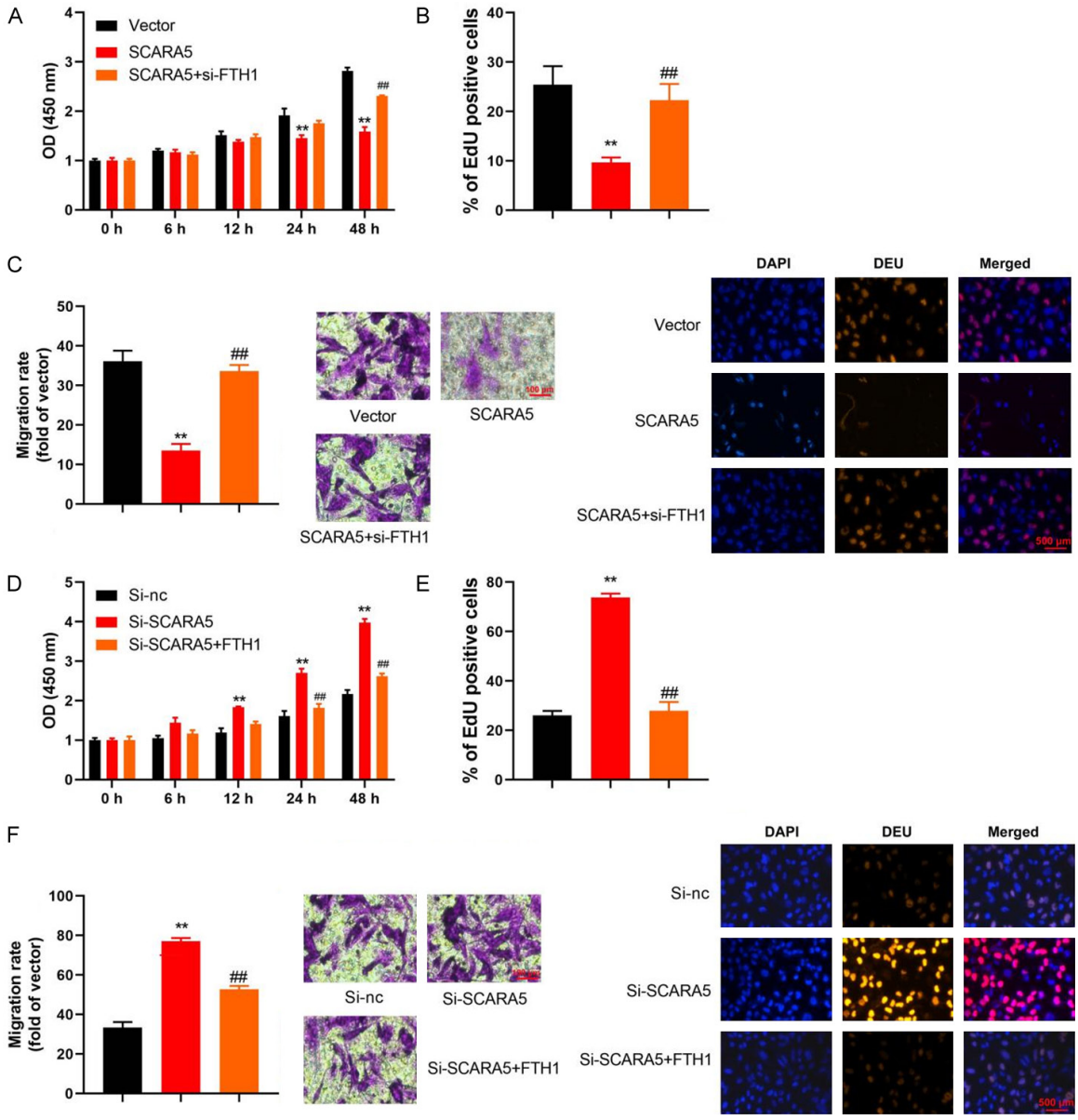

Figure 7. Si-FTL reduced the effects of SCARA5 on cell growth of colon cancer. Cell growth (A and D); EDU assay (B and E, scale bar = 500 μm), migration rate (C and F, scale bar = 100 μm) in vitro model of colon cancer. **P<0.01 compared with negative group or si-negative group; ##P<0.01 compared with SCARA5 up-regulation group or SCARA5 down-regulation group.

incomplete link to SCARA5 protein (**Figure 9B**). Subsequently, SCARA5 up-regulation reduced FTL protein ubiquitination, and SCARA5 down-regulation promoted FTL protein ubiquitination (**Figure 9C**).

Discussion

In its early stages, symptoms primarily encompass abdominal pain, bloating, constipation, and bloody stools [20, 21]. Although advancements have been witnessed in radiotherapy, chemotherapy, immunotherapy, and targeted therapy for CC in recent years, it remains highly prone to hematogenous metastasis, with liver metastasis being the predominant manifestation [22]. According to the statistical data of the American Cancer Society in 2023, although a large part of colorectal cancer deaths can be prevented through screening, and the overall mortality continues to decline, the decline in its incidence rate is slowing down, and its diagno-

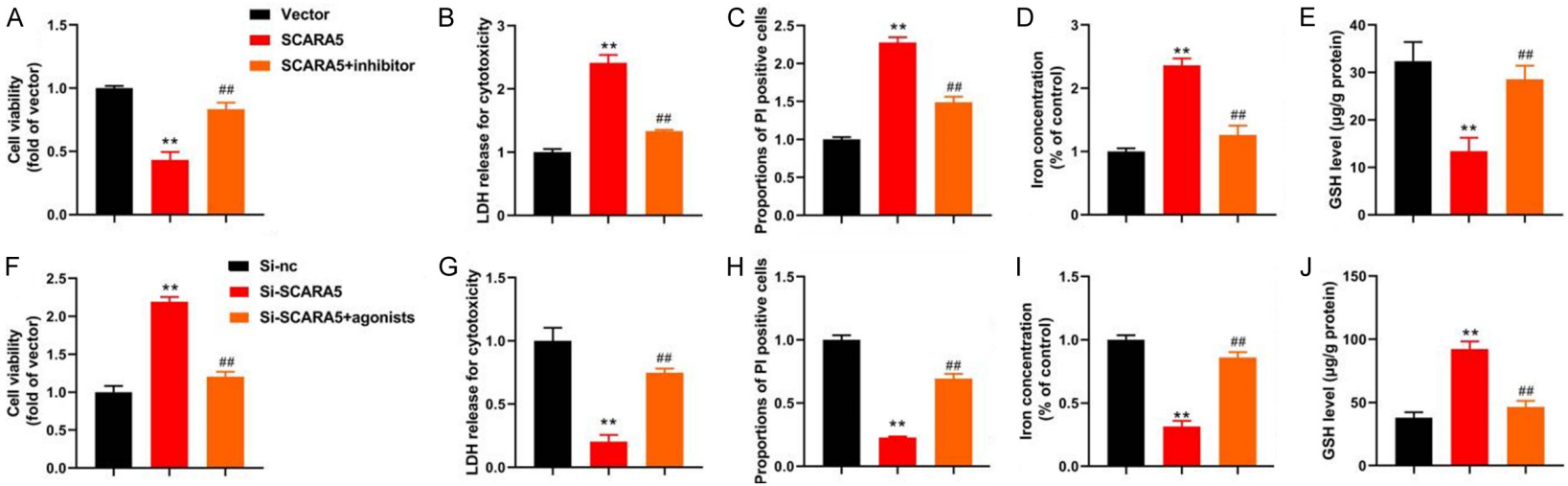

Figure 8. Ferroptosis is one factor for SCARA5 on colon cancer. Cell growth (A and F); LDH activity levels (B and G), PI cell (C and H), iron content (D and I), GSH activity levels (E and J). **P<0.01 compared with negative group or si-negative group; ##P<0.01 compared with SCARA5 up-regulation group or SCARA5 down-regulation group.

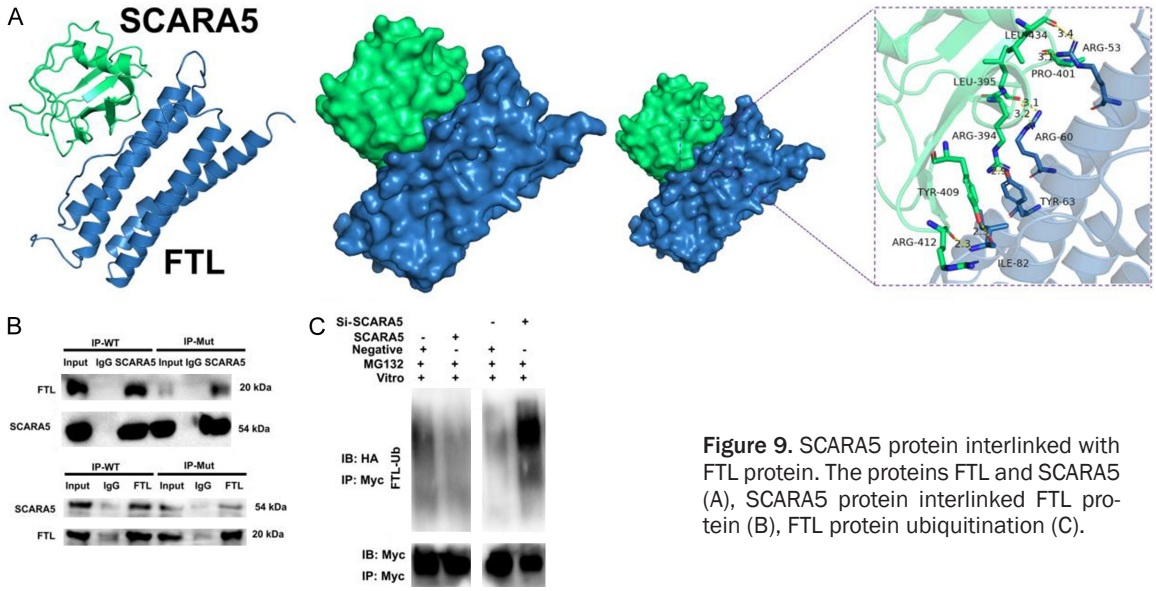

Figure 9. SCARA5 protein interlinked with FTL protein. The proteins FTL and SCARA5 (A), SCARA5 protein interlinked FTL protein (B), FTL protein ubiquitination (C).

sis is rapidly shifting to younger, more advanced and left rectum, suggesting the potential disease risk of unknown etiology [23, 24]. The mortality rate of CC is high, and the treatment of advanced CC mainly involves surgery combined with chemotherapy. Within this subset, approximately 80-90% are disqualified for radical resection, accompanied by a dismal 5-year survival rate, constituting a clinical conundrum and a critical therapeutic focus [25]. The ongoing investigation has discerned a reduction in SCARA5 mRNA expression levels among CC patients. Sh-SCARA5 promoted CC in mice model. SCARA5 up-regulation reduced cell growth of CC. SCARA5 impedes the cellular progression of gastric cancer [14]. Collectively, these data suggest that involvement of SCARA5 in the disease trajectory of CC.

It is iron dependent and is caused by oxidation induced by small molecule substances. GPX4 belongs to phospholipid hydroperoxide GPX and is one of the key proteins involved in ferroptosis. There are literature reports that GPX4 is associated with oxidation reactions and may be a potential regulator of iron death [26]. Studies have demonstrated that Ferroptosis can be elicited under diverse physiological conditions and pathological stress, exerting a crucial role in tumorigenesis [27]. Our research uncovered that the upregulation of SCARA5 facilitated Ferroptosis in CC through the induction of mitochondrial damage. SCARA5 induced ferroptosis of esophageal squamous cell carcinoma [17]. These data indicated that SCARA5 promoted Ferroptosis in CC through the induction of mitochondrial damage.

FTH possesses iron oxidase activity, which facilitates the rapid absorption and release of iron, while FTL contributes to the long-term storage of iron FTL plays a role in the growth and migration of CC cells, potentially associated with alterations in iron homeostasis within cancer [10, 28, 29]. In CC cells, high expression of H-ferritin rather than L-ferritin, results in approximately a 50% in cell apoptosis, and this anti apoptotic activity is not related to iron oxidase activity [30]. We demonstrated that the SCARA5 protein interacts with FTL protein, and the upregulation of SCARA5 reduces FTL protein ubiquitination. Liu et al. validated that SCARA5 binds to FTL protein expression in Esophageal squamous cell carcinoma [17]. Consequently, SCARA5 reduces the ubiquitination of the FTL protein to induce FTL expression in CC.

Based on these discoveries, we infer that SCARA5 promoted ferroptosis in CC by inducing mitochondrial damage by FTL protein ubiquitination, and the application of SCARA5 may confer benefits in the treatment of CC.

Disclosure of conflict of interest

None.

Abbreviations

FTL, ferritin light chain; FTH, ferritin heavy chain; SCARA5, Scavenger receptor class A member 5; CRC, Colorectal cancer; CC, colon cancer; EdU, Ethynyl deoxyuridine; DFS, disease-free survival.

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