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Upregulation of SIRT6 enhances autophagy-dependent ferroptosis of colorectal cancer cells through inactivating the mTOR/STAT3 signaling pathway

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Accumulating evidence highlights the critical roles of autophagy-dependent ferroptosis mediators in colorectal cancer (CRC) pathogenesis. To elucidate SIRT6's tumor-suppressive role, HT29 cells stably overexpressing SIRT6 (Oe-SIRT6) were generated via plasmid transfection. Functional assays were performed to evaluate autophagy and ferroptosis. Rescue experiments using the autophagy inhibitor 3-MA or the mTOR agonist MHY1485 were conducted. Quantitative analyses revealed marked downregulation of SIRT6 expression in CRC cell lines (SW620, SW480, and HT29) compared to normal colon epithelial cells. SIRT6 overexpression induced autophagy and activated ferroptosis. The autophagy inhibitor 3-MA blocked SIRT6-driven ferroptosis, which confirmed its dependency on autophagy. Moreover, SIRT6 was found to inactivate mTOR/STAT3 signaling, whereas the mTOR agonist MHY1485 reversed SIRT6 overexpression on autophagy-dependent ferroptosis of CRC cells. Our findings establish SIRT6 as a dual-phase regulator of CRC cell death, suppressing mTOR/STAT3 signaling to orchestrate autophagy-dependent ferroptosis.

Key words: SIRT6, autophagy-dependent ferroptosis, mTOR/STAT3 signaling pathway, colorectal cancer

Colorectal adenocarcinoma (CRC) persists as a leading cause of cancer-related morbidity and mortality worldwide [1]. Despite multimodal therapeutic regimens integrating surgery, chemotherapy, and radiotherapy, disease recurrence and therapeutic resistance remain formidable clinical challenges. These limitations underscore the urgent need for innovative strategies targeting alternative cell death pathways [2].

Ferroptosis is a recently identified, iron-dependent form of cell death [3]. The mammalian target of rapamycin (mTOR) inhibits autophagy-dependent ferroptosis by suppressing NCOA4-mediated ferritinophagy [4]. Meanwhile, signal transducer and activator of transcription 3 (STAT3) activation downregulates glutathione peroxidase 4 (GPX4), thereby potentiating ferroptotic death [5]. As SIRT6 has been shown to modulate mTOR in other cancers [6], we hypothesize that it may also play a role in CRC. However, direct evidence linking this regulatory network to autophagy-ferroptosis crosstalk in CRC remains limited. Recent evidence suggests that ferroptotic cell death may be facilitated by the autophagic machinery [7, 8]. Consequently, ferroptosis is now recognized as a process that depends on and is regulated by autophagy.

There are seven members of the Sirtuin family (SIRT1-7), which are histone deacetylases that rely on nicotinamide adenine dinucleotide (NAD+) [9]. SIRT6 is a nuclear sirtuin that primarily acts in the metabolism of energy from glucose and lipids, DNA repair, aging, inflammation, and immunity [10, 11]. According to recent research, SIRT6 can either act as a tumor suppressor or an oncogene in various human cancers [12]. In CRC, SIRT6 is markedly downregulated in neoplastic tissues compared to normal epithelia, with its loss correlating with accelerated proliferation, chemoresistance, and poor survival outcomes [13, 14]. However, its regulatory interplay with autophagy-ferroptosis crosstalk remains unexplored.

The rapamycin (mTOR) pathway is frequently dysregulated in CRC and plays a critical role in cell proliferation and metastasis [15]. It has become a desirable therapeutic target for CRC [16]. In response to cytokines, STAT3, a member of the STAT family, is phosphorylated by receptor-associated kinase and then translocated to the nucleus [17]. Through the transcriptional control of many autophagy-related genes, the mTOR and STAT3 pathways negatively regulate autophagy [17, 18]. Besides, there is a crosstalk between the mTOR and STAT3 signaling pathways in regulating autophagy [19,

20]. In this study, we elucidate a novel tumor-suppressive axis wherein SIRT6 drives autophagy-dependent ferroptosis in CRC through mTOR/STAT3 pathway inactivation. Our findings provide a mechanistic rationale for therapeutic targeting of this pathway to overcome CRC therapy resistance.

Materials and methods

Cell lines and cell culture. Normal colon epithelial cell line NCM460 and human CRC cell lines SW620 and SW480 were obtained from Cellverse (Shanghai, China). HT29 and HCT116 cells were sourced from the American Type Culture Collection (ATCC, USA). Cells were maintained in RPMI-1640 (NCM460, HCT116, HT29) or DMEM (SW620, SW480) supplemented with 10% FBS (v/v) and 1% penicillin-streptomycin (Gibco) at 37 °C under 5% CO_2.

Transfection and drug treatment. The full-length human SIRT6 cDNA was subcloned into the pcDNA3.1(+) vector (GenePharma, Shanghai, China) for stable overexpression (Oe-SIRT6). HT29 cells (2×10^5 cells/well in 6-well plates) were transfected with 2 μg plasmid DNA using Lipofectamine 2000 (Invitrogen, USA) for 48 h, per manufacturer's guidelines.

HT29 cells were divided into five groups as designed: 1) Control group receiving no treatment; 2) Oe-NC group; 3) Oe-SIRT6 group; 4) Oe-SIRT6+3-methyladenine (3-MA) (2.5 mM, autophagy inhibitor; MedChemExpress, USA) group; 5) Oe-SIRT6 + MHY1485 (10 μM, mTOR agonist; MedChemExpress, USA) group. Treatments were administered 24 h post-transfection for 48 h.

Immunofluorescence (IF) staining. Cells were fixed in 4% paraformaldehyde (PFA) for 15 min, permeabilized with 0.1% Triton X-100 (10 min), and blocked with 5% BSA (1 h, room temperature). Primary anti-LC3 antibody (1:200; Abcam, #ab192890) was incubated overnight at 4 °C, followed by FITC-conjugated secondary antibody (1:500; Abcam, #ab6717) for 1 h. Nuclei were counterstained with DAPI (Sigma-Aldrich), and images were acquired using a Leica DMi8 fluorescence microscope.

RT-qPCR. Prime Script RT reagent kit (Takara, RR037A) was used to reverse-transcribe total RNA isolated from cells using TRIzol® reagent into cDNA. The SYBR Green PCR Kit (Thermo Fisher, 4306736) was then used in a qPCR experiment on an ABI 7500 quantitative PCR instrument. SIRT6 relative mRNA expression was calculated using the $2^{-\Delta\Delta Cq}$ method.

Western blot assay. Using the RIPA buffer (Beyotime, #P0013B) to extract total protein from cells, the BCA was used to quantify the protein content. SDS-PAGE was used to separate protein samples (30 μg/lane), which were then transferred to PVDF membranes. After blocking in 5% BSA for 1 h at 37 °C, PVDF membranes were incubated on a shaker with primary antibodies against SIRT6 (1:1000, Abcam, #ab191385), p62 (1:1000, Abcam, #ab109012), ATG5 (1:1000, Abcam, #ab108327), ATG7 (1:1000, Abcam, #ab52472), LC3-II/I (1:1000, Merck, #ABC929), ACSL4 (1:1000, Abcam, #ab155282), GPX4 (1:1000, Abcam, #ab125066), FTH1 (1:1000, Abcam, #ab75973), SLC7A11 (1:1000, Merck, #SAB2500951), NCOA4 (1:1000, Abcam, #ab314553), p-mTOR (1:1000, Abcam, #ab109268), mTOR (1:1000, Abcam, #ab134903), p-STAT3 (1:1000, Abcam, #ab267373), STAT3 (1:1000, Abcam, #ab68153) and GAPDH (1:1000, Abcam, #ab8245) overnight at 4 °C and then incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. GAPDH served as the internal control. Blots were developed using an ECL kit (Beyotime, #P0018S) and quantified via ImageJ.

Determination of total iron. Total iron level in the supernatant of HT29 cells was measured using the Iron Assay Kit (Beyotime, #S1070S) according to the manufacturer's guidelines.

Measurement of lipid ROS. Intracellular lipid ROS generation was measured by the BODIPY 581/591 C11 probe. Following 30 min dark incubation period at 37 °C with 10 μM BODIPY 581/591 C11, images of the stained HT29 cells were captured using a fluorescence microscope.

Measurement of MDA and 4-HNE. Levels of MDA and 4-HNE in the supernatant of HT29 cells were measured using corresponding commercial biochemical kits (MDA, Abcam, #ab118970; 4-HNE, Abcam, #ab238538) following the manufacturer's guidelines.

Statistical analysis. Data are presented as mean ± SD. Comparisons among multiple groups were analyzed by one-way ANOVA with Tukey's post-hoc test (GraphPad Prism 9.0). Statistical significance was set at $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Results

SIRT6 is lowly expressed in CRC cells. We compared the levels of SIRT6 expression between the normal colonic epithelial cell line, NCM460, and four human CRC cell lines: SW620, SW480, HCT116, and HT29. All CRC cell lines exhibited significantly reduced levels of SIRT6 mRNA (Figure 1A) and protein (Figure 1B) compared to NCM460 cells. HCT116 cells exhibit an intermediate expression of SIRT6 and a high microsatellite instability (MSI-H) phenotype. HT29 cells showed the most pronounced decrease, which justified their selection for functional assays. Subsequent experiments were therefore conducted using the HT29 cell line.

SIRT6 overexpression enhances autophagy in CRC cells. For gain-of-function experiments, Oe-SIRT6 cells expressed higher SIRT6 vs. NCM460 normal cells, and HT29 cells were transfected with Oe-SIRT6 to significantly upregulate SIRT6 expression (Figures 2A, 2B). Oe-SIRT6-transfected cells exhibited elevated levels of autophagy markers, including LC3 accumulation, ATG5, ATG7, and LC3-II/LC3-I ratio, alongside reduced p62 expression

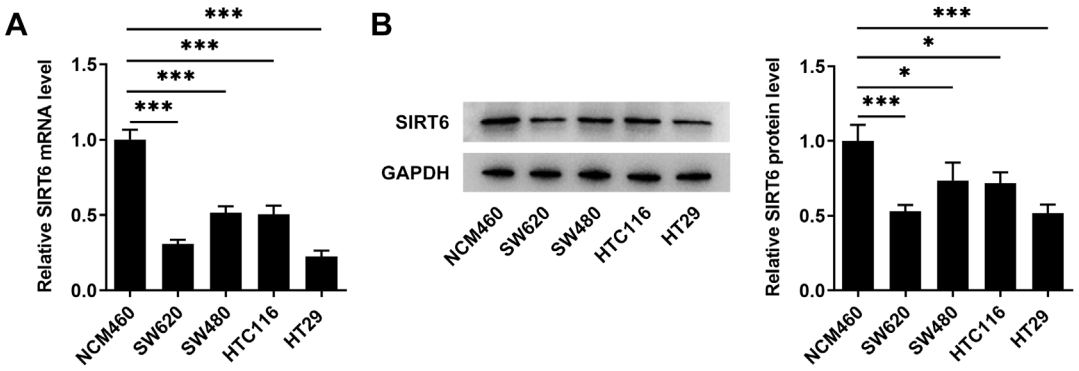

Figure 1. SIRT6 is lowly expressed in CRC cells. A, B) Expression differences of SIRT6 in normal colon epithelial cell line NCM460 and human CRC cell lines SW620, SW480, HCT116, and HT29 were detected by RT-qPCR and western blot. *p<0.05, ***p<0.001

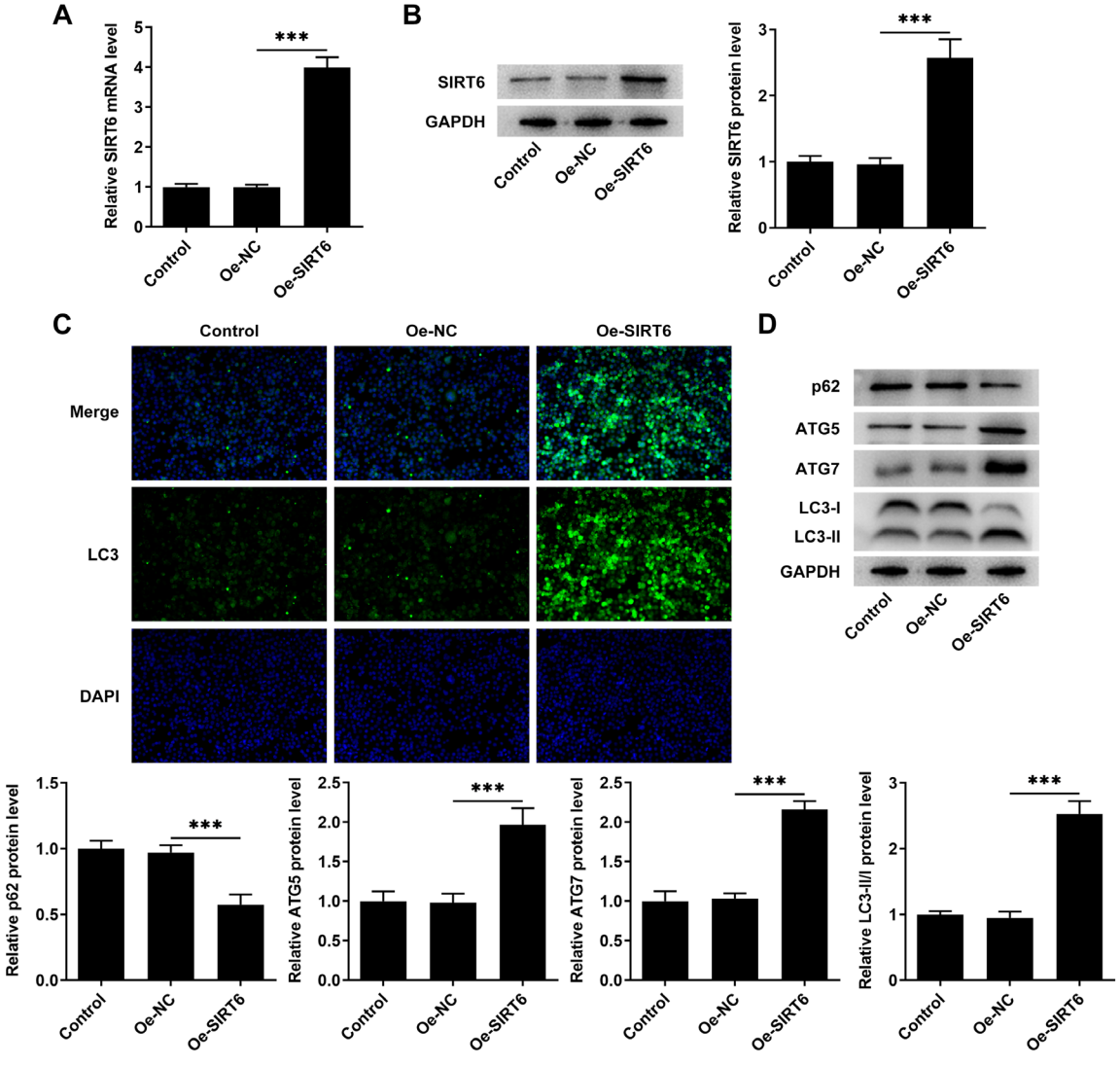

Figure 2. SIRT6 overexpression enhances autophagy in CRC cells. HT29 cells were transfected with Oe-SIRT6 or Oe-NC. A, B) Transfection efficiency of Oe-SIRT6 in HT29 cells was validated by RT-qPCR and western blot. C) LC3 expression was evaluated by IF staining. D) Expressions of p62, ATG5, ATG7, and LC3 II/I were detected by western blot. ***p<0.001

(Figures 2C, 2D), demonstrating that SIRT6 enhances autophagic activity in CRC cells.

SIRT6 overexpression enhances autophagy-dependent ferroptosis of CRC cells. Elevated total iron content, intracellular lipid ROS generation, as well as levels of lipid peroxides MDA and 4-HNE in HT29 cells transfected with Oe-SIRT6 indicated that SIRT6 overexpression promoted ferroptosis of HT29 cells (Figures 3A–3C). Mechanistically, Oe-SIRT6 cells exhibited increased ACSL4 and NCOA4 expression alongside reduced GPX4, FTH1, and SLC7A11 levels, further

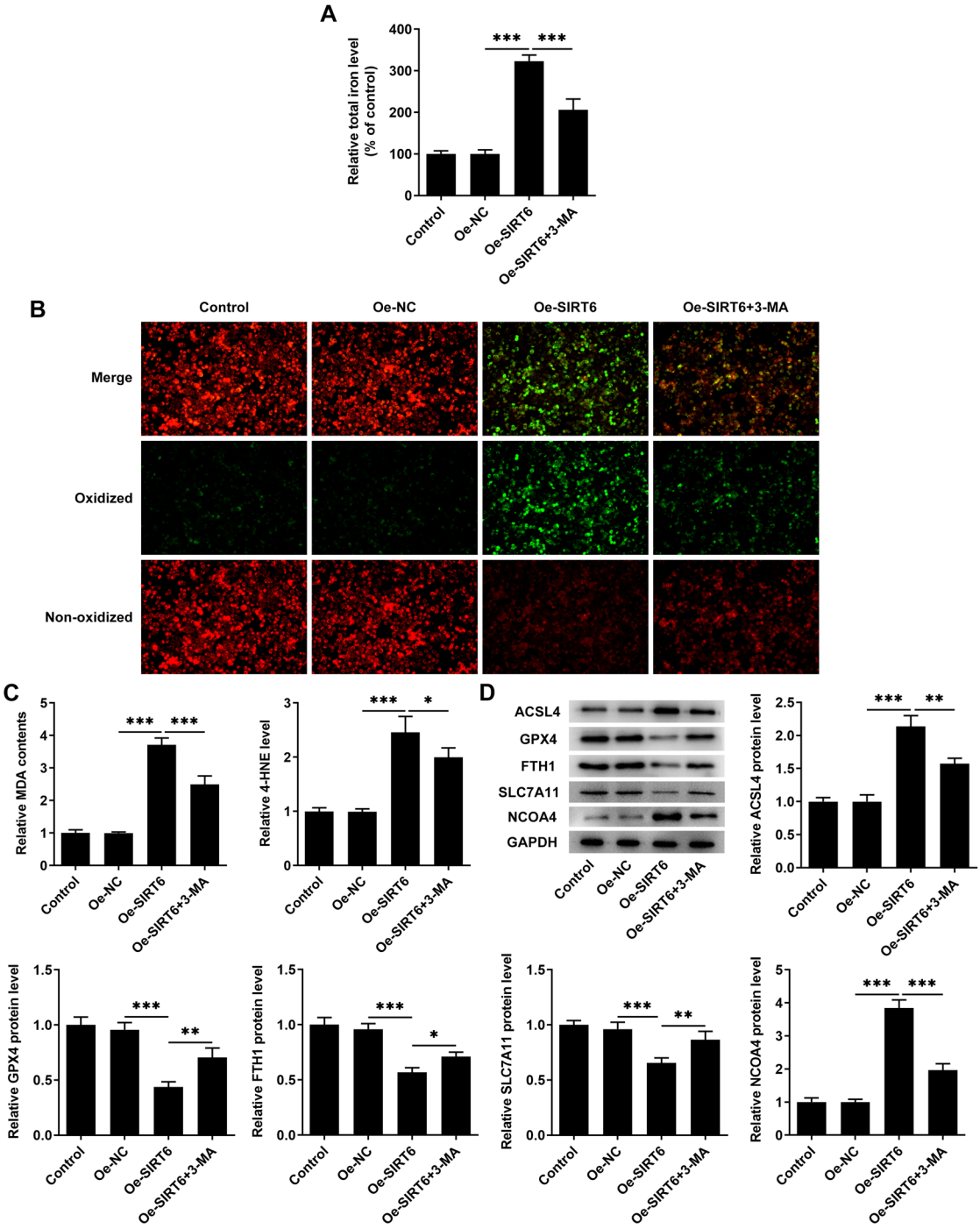

Figure 3. SIRT6 overexpression enhances autophagy-dependent ferroptosis of CRC cells. HT29 cells transfected with Oe-SIRT6 were treated with the autophagy inhibitor 3-MA. A) Total iron level was detected using an iron assay kit. B) Intracellular lipid ROS generation was detected by the BODIPY 581/591 C11 probe. C) MDA and 4-HNE levels were detected using the corresponding commercial biochemical kits. D) Expressions of ACSL4, GPX4, FTH1, SLC7A11, and NCOA4 were detected by western blot. *p<0.05, **p<0.01, ***p<0.001

confirming enhanced ferroptotic susceptibility (Figure 3D). Furthermore, treatment with the autophagy inhibitor 3-MA suppressed ferroptosis of HT29 cells, as evidenced by reduced total iron accumulation, lipid ROS production, and peroxidation markers, decreased expressions of ACSL4 and NCOA4, as well as increased expressions of GPX4, FTH1, and SLC7A11 in HT29 cells transfected with Oe-SIRT6. In summary, these findings collectively demonstrate that SIRT6 upregulation promotes autophagy-dependent ferroptosis in CRC cells.

SIRT6 overexpression inactivates the mTOR/STAT3 signaling pathway in CRC cells. To investigate whether SIRT6 overexpression exerts anti-tumorigenic effects by mediating the mTOR/STAT3 signaling pathway, we examined the key proteins involved in this pathway. The reduced expression of p-mTOR and p-STAT3 in Oe-SIRT6 cells indicated inhibi-

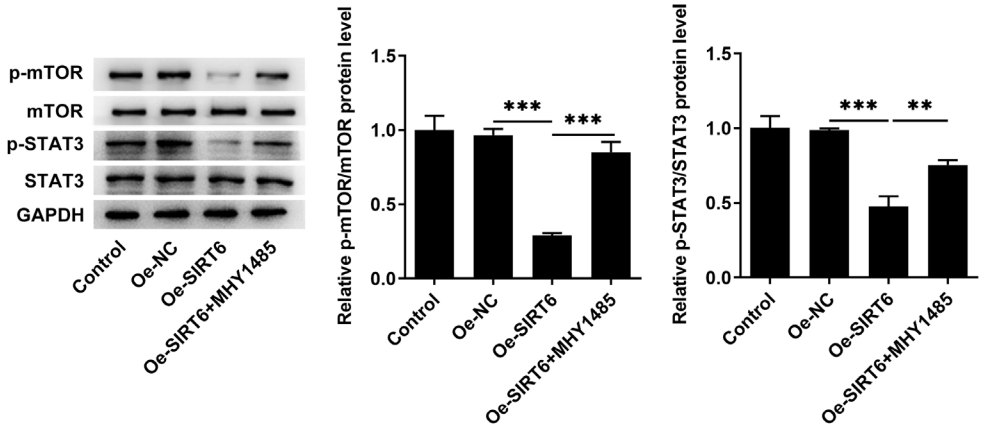

Figure 4. SIRT6 overexpression inactivates the mTOR/STAT3 signaling pathway in CRC cells. HT29 cells transfected with Oe-SIRT6 were treated with mTOR agonist MHY1485. Expressions of p-mTOR, mTOR, p-STAT3, and STAT3 were detected by western blot. **p<0.01, ***p<0.001

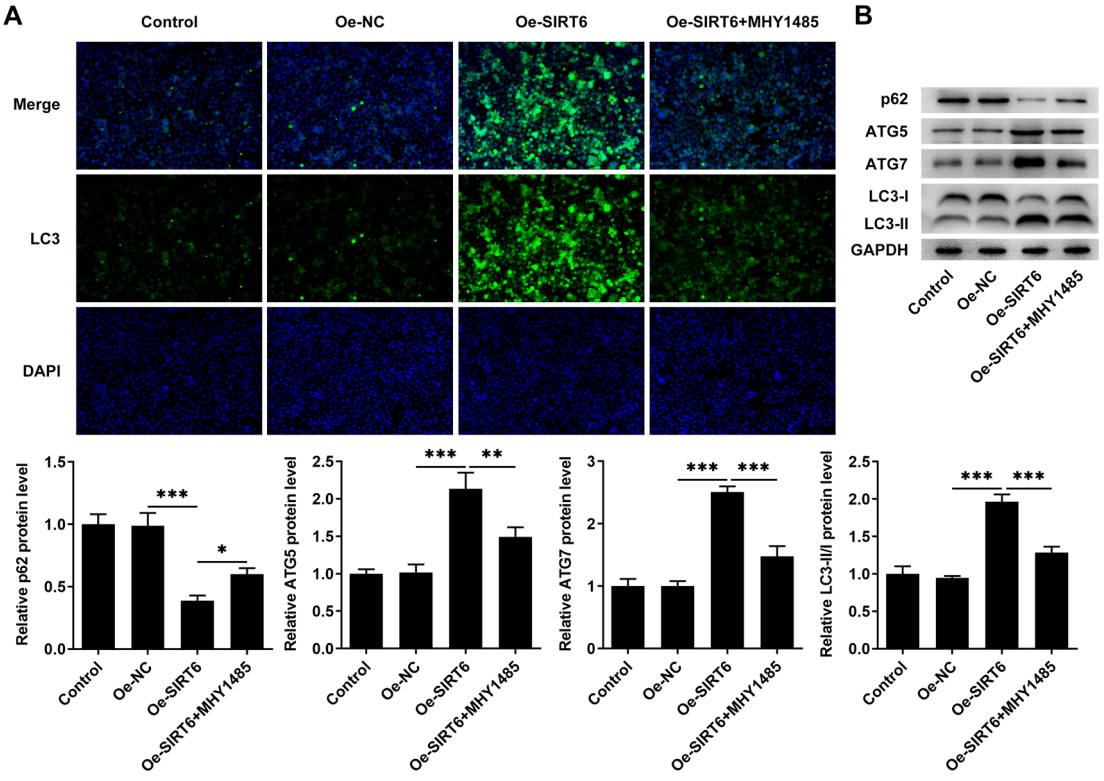

Figure 5. SIRT6 overexpression enhances autophagy in CRC cells by inactivating the mTOR/STAT3 signaling pathway. HT29 cells transfected with Oe-SIRT6 were treated with mTOR agonist MHY1485. A) LC3 expression was evaluated by IF staining. B) Expressions of p62, ATG5, ATG7, and LC3 II/I were detected by western blot. *p<0.05, **p<0.01, ***p<0.001

tion of the mTOR/STAT3 pathway. Apparently, treatment with mTOR agonist MHY1485 activated the mTOR/STAT3 signaling pathway in HT29 cells transfected with Oe-SIRT6 (Figure 4).

SIRT6 overexpression enhances autophagy in CRC cells by inactivating the mTOR/STAT3 signaling pathway. Treatment with the mTOR agonist MHY1485 reduced LC3 accumulation, decreased protein levels of ATG5, ATG7, and the LC3-II/LC3-I ratio, and elevated p62 levels in HT29 cells transfected with Oe-SIRT6, partially reversing the strengthening effects of SIRT6 overexpression on autophagy in HT29 cells (Figures 5A, 5B). In a word, these findings show that SIRT6 overexpression enhances autophagy in CRC cells by suppressing the mTOR/STAT3 signaling.

SIRT6 overexpression enhances autophagy-dependent ferroptosis of CRC cells through inactivating the mTOR/STAT3 signaling pathway. Treatment with MHY1485 in Oe-SIRT6-transfected HT29 cells reduced total iron content, lowered intracellular lipid ROS generation, and decreased levels of MDA and 4-HNE. It also downregulated ferroptosis-promoting proteins ACSL4 and NCOA4 while upregulating ferroptosis suppressors GPX4, FTH1, and SLC7A11 (Figures 6A–6D). These changes partially reversed the enhancing effects of SIRT6 overexpression, confirming that SIRT6 enhances autophagy-dependent ferroptosis in CRC cells through the mTOR/STAT3 pathway inactivation.

Discussion

CRC is a complex and heterogeneous disease characterized by multiple molecular alterations [21]. The tumor suppressor role of SIRT6 in CRC may be driven by epigenetic silencing [22]. This study found that silencing SIRT6 promotes early tumor development, but advanced tumors under metabolic stress may reactivate SIRT6 to encourage treatment resistance [23]. We propose CRC early loss drives tumorigenesis, whereas late re-expression promotes treatment resistance. Notably, SIRT6 expression is downregulated in CRC cells and tissues [13, 14], where it regulates fatty acid β-oxidation [24], drug resistance [25], and oncogenic processes such as proliferation and metastasis [14]. Consistently, decreased SIRT6 expression in CRC cells was also confirmed in our current work. Importantly, SIRT6 overexpression induced autophagy and ferroptosis in CRC cells. Mechanistically, our research shows that the SIRT6-ferroptosis mechanism identified in MSS HT29 cells from non-metastatic CRC may not apply to the MSI-H subtype. The effects of SIRT6 may be attenuated by persistent mTOR activation caused by PIK3CA mutations.

Autophagy is closely associated with malignant transformation in cancer [26]. Previous research has indicated that autophagy plays a dual role in CRC tumorigenesis [27] and chemoresistance [28]. Notably, SIRT6 enhances autophagic activity by directly interacting with ULK1 and competitively inhibiting PUMA binding [6]. Overexpression of SIRT6 has been shown to inhibit GLUT1 through autophagy-mediated degradation, thereby ultimately suppressing the Warburg effect in thyroid cancer [29]. In our experiments, we observed that in HT29 cells with SIRT6 overexpression, the levels of LC3-II/I, ATG5, and ATG7 protein increased, while the levels of p62 protein decreased, suggesting that SIRT6 overexpression may promote autophagy in CRC cells.

Autophagy is closely linked to ferroptosis. Autophagy disrupts iron homeostasis by degrading ferritin through the NCOA4 pathway, elevating labile iron pools that potentiate ferroptosis [30]. In CRC, it was shown that Circ_0087851 suppresses CRC progression by inducing miR-593-3p/BAP1-dependent ferroptosis [31]. Additionally, TRIM36-mediated FOXA2 can promote CRC progression by suppressing the Nrf2/GPX4 ferroptosis signaling pathway [32]. Ferroptic death plays a dual role in the pathogenesis of CRC: its activation can remodel the tumor microenvironment through oxidative stress and immune regulation, while resistance to ferroptic death is associated with chemotherapy failure. Studies have shown that low GPX4 expression levels are significantly associated with prolonged overall survival in CRC patients [33]. Notably, reduced GPX4 expression in CRC is positively correlated with oxaliplatin sensitivity [34], suggesting that inducing iron death holds therapeutic potential. The SIRT6-driven ACSL4/NCOA4 activation mechanism revealed in this study provides biomarker-guided therapeutic strategies for restoring chemotherapy sensitivity by enhancing the iron death pathway. Critically, SIRT6 overexpression in CRC cells elevates lipid peroxidation and ferroptosis markers, effects partially reversed by the autophagy inhibitor 3-MA. Consequently, these findings demonstrate that SIRT6 promotes ferroptosis in CRC in an autophagy-dependent manner, underscoring metabolic crosstalk as a therapeutic target. Despite the lack of *in vivo* models, there is clinical evidence to support our findings. Patients with CRC who exhibited low GPX4 expression had a longer median survival time [33].

Previous research showed the mTOR pathway suppressed autophagy-dependent ferroptosis. Moreover, STAT3 signaling exacerbates cardiac injury in high-fat diet-fed mice by driving NCOA4-mediated ferritinophagy and ferroptosis [35]. In the current research, baicalein induces ferroptosis in CRC cells by inhibiting the JAK2/STAT3/GPX4 axis [5]. Similarly, SERPINH1 enhances CRC proliferation and metastasis via activation of the PI3K/Akt/mTOR pathway [15]. Through investigation, mTOR activator MHY1485 was also proven to counteract the intensified autophagy and ferroptosis of CRC cells transfected with Ov-SIRT6.

In conclusion, our findings support a model wherein SIRT6 suppresses the mTOR/STAT3 signaling pathway, triggering autophagy-dependent ferroptosis in CRC cells. Collectively, these data define a novel tumor-suppressive mechanism in which SIRT6 activation induces iron-dependent cell death through coordinated inhibition of pro-survival mTOR/STAT3 signaling and autophagic flux potentiation.

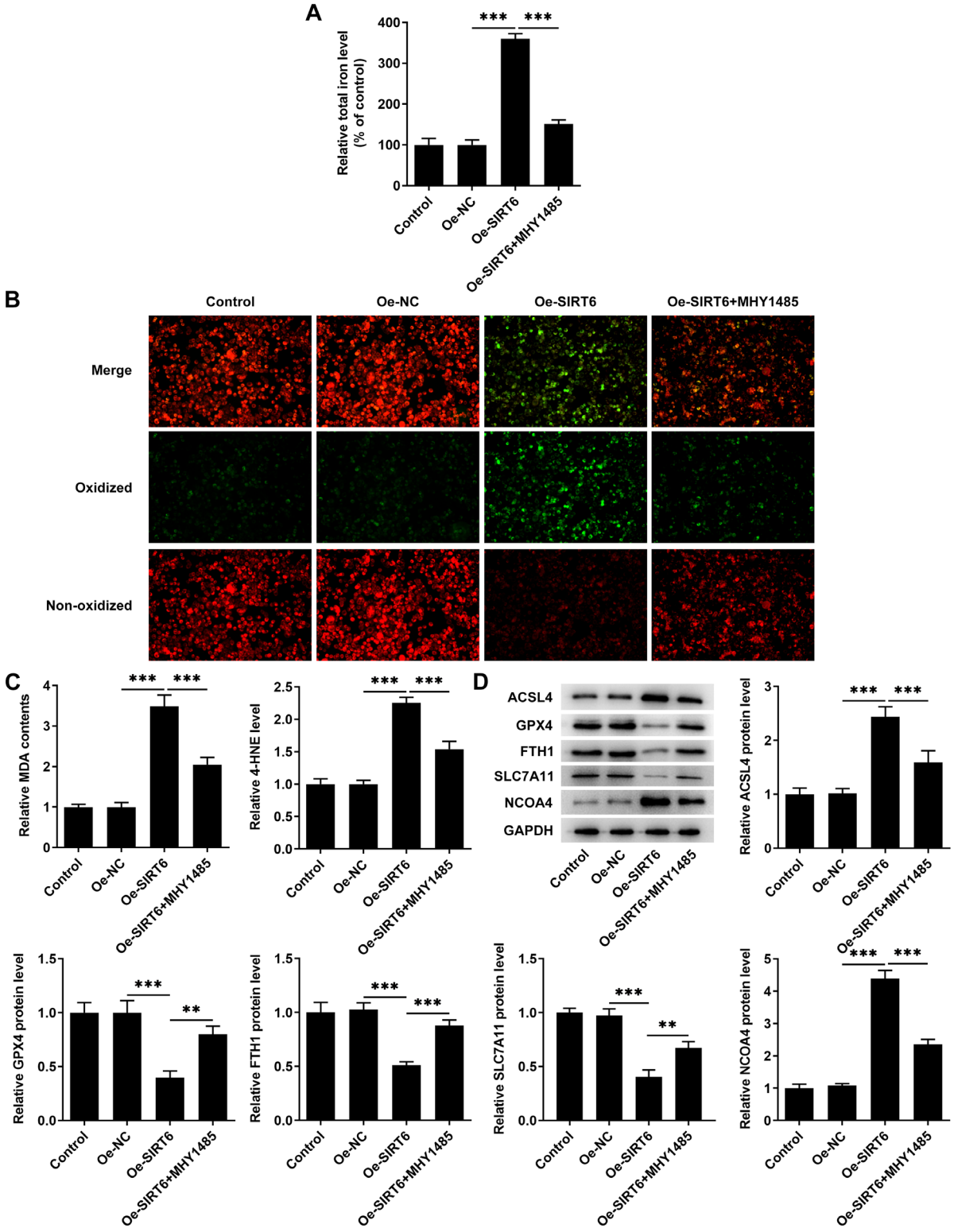

Figure 6. SIRT6 overexpression enhances autophagy-dependent ferroptosis of CRC cells through inactivating the mTOR/STAT3 signaling pathway. HT29 cells transfected with Oe-SIRT6 were treated with mTOR agonist MHY1485. A) Total iron level was detected using an iron assay kit. B) Intracellular lipid ROS generation was detected by the BODIPY 581/591 C11 probe. C) MDA and 4-HNE levels were detected using the corresponding commercial biochemical kits. D) Expressions of ACSL4, GPX4, FTH1, SLC7A11, and NCOA4 were detected by western blot. **p<0.01, ***p<0.001

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