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ORIGINAL ARTICLE

SARS-CoV-2 N protein interacts with SLC7A11 to cause ferroptosis in acute lung injury

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KEYWORDS
SARS-CoV-2;
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Abstract
Background: The nucleocapsid protein (N protein) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is elevated in bodily fluids at the onset of infection and has recently been found to have a direct role in lung damage. However, the exact mode of action of the N protein in acute lung injury is still unknown.
Method: Recombinant N protein was used to treat mice and A549 cells in vivo and in vitro. Enzyme-linked immunosorbent assay and hematoxylin and eosin staining were used to detect the levels of inflammatory factors and lung damage in lung tissue. The total iron and Fe^{2+} contents and the expression of ferroptosis markers in mouse lung tissues and cells were detected. Co-immunoprecipitation detects the binding of N protein and solute carrier family 7 member 11 (SLC7A11). Replenishment experiments were conducted by activating SLC7A11 to study the effect of SLC7A11 on N protein-induced lung injury.
Result: Recombinant N protein caused acute lung injury and lung inflammation, increased total iron and Fe^{2+} contents in vivo and in vitro, promoted the expression of ACSL4, inhibited the expression of GPX4 and FTH1, and triggered ferroptosis. Recombinant N protein can interact with SLC7A11, and activating SLC7A11 can reverse N protein-induced ferroptosis and acute lung injury.
Conclusion: SARS-CoV-2 N protein can directly interact with SLC7A11 to cause ferroptosis, which produces a lot of inflammatory factors and results in lung injury in mice.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that triggered the coronavirus disease (COVID-19) epidemic worldwide has dealt a huge blow to the public health and the economy.[1,2] The most severe and common adverse effects of COVID-19 are acute respiratory distress syndrome and acute lung injury.[3] Early diffuse alveolar damage is a hallmark of SARS-CoV-2-induced acute lung injury. In more severe cases, late epithelial cells lose their capacity to repair, which results in respiratory failure.[4] However, the precise mechanism causing acute lung injury caused by SARS-CoV-2 is still unknown.

The viral envelope is held together by three of four structural proteins: spike (S), membrane (M), and envelope (E) proteins. The fourth structural protein is the nucleocapsid protein (N protein), which is located within the viral envelope and encapsulates the RNA genome in a helical ribonucleoprotein complex and is essential for viral infection and replication.[5,6] Numerous investigations have demonstrated that SARS-CoV-2N contributes to ferroptosis and is directly linked to acute lung damage. For instance, the SARS-CoV-2 N protein alters macrophage activation and infiltration both in vivo and in vitro, resulting in acute lung damage.[7] By triggering NF- κB, the SARS-CoV-2 N protein causes acute lung damage in mice.[8] On the other hand, necroptosis and ferroptosis caused by the SARS-CoV-2 virus may have a new mechanism, both of which could have a role in influencing how the infection turns out.[9] The SARS-CoV-2 accessory protein Orf7b causes lung damage by causing ferroptosis and apoptosis mediated by c-Myc.[10] Through the Keap1-NRF2 axis, SARS-CoV-2 ORF3a makes cells more susceptible to ferroptosis.[11]

SLC7A11, the catalytic subunit of the amino acid transport system Xc-, is a member of the solute carrier family. The SLC7A11 system is the primary regulator of the cellular ferroptosis defense mechanism and the primary defense against ferroptosis.[12,13] Several research teams have suggested that SLC7A11 may have a part in the pathophysiology of COVID-19.[14,15]

In this study, we intended to evaluate whether SLC7A11 is a receptor for N protein and determine the influence of N protein-SLC7A11 interaction on ferroptosis in acute lung damage.

Methods

Mice and treatment

The animal study protocol was preapproved by the Institutional Animal Care and Use Committee of Second Affiliated Hospital of Chongqing Medical University (number: 2021(440)). We used Shanghai Experimental Animal Center's C57BL/6 mice. Twelve mice were randomly divided in two groups (six per group). Mice were raised under specific pathogen-free conditions and maintained at constant temperature and humidity. An intraperitoneal injection of phenobarbital (50 mg/kg) was used to put the mice to sleep. Acute lung injury was caused by injecting 80 μL of PBS/mouse or an equivalent amount of PBS intratracheally along with recombinant N protein (4 mg/kg, GenScript, Nanjing, China).[7] The effect of SLC7A11 on N protein–induced lung injury was investigated by injecting the tail veins of mice with a total of 1×10^8 PFU SLC7A11 overexpression adenovirus. Lung tissue from mice was extracted after 24 hours.

Histopathology

The lung tissue that was harvested was preserved, encased in paraffin, and then sliced into 5-μm thick sections. Hematoxylin and eosin (H&E) was used to stain the sections. Nikon VS120 microscope (Shinjuku, Tokyo, Japan) was used to take pictures of the lung sections.

Enzyme-linked immunosorbent assay (ELISA)

Samples of lung tissue were taken and promptly stored at −80°C. Lung tissue can be examined for inflammatory factors using an ELISA kits (Beyotime). The levels of Interleukin 6 (IL-6), IL-β, and tumor necrosis factor alpha (TNF-α) were measured according to the instructions of the manufacturer.

Cell culture and treatment

The American Type Culture Collection is where the human lung epithelial cells (A549) were acquired. Eagle's medium modified by Dulbecco was used to cultivate A549 cells. Ten percent fetal calf serum was added to each medium, which was then kept at 37°C in an incubator with 5% CO_2. All reagents are from Sigma-Aldrich. After that, cells were exposed to recombinant N protein for 24 hours at a concentration of 5 μg/mL.[8] Prior to treatment with recombinant N protein, SLC7A11 cDNA was subcloned into pAAV-CMS vector, and Lipofectamine 3000 (Thermo Fisher Scientific) was used to transfect oe-SLC7A11 into A549 cells.

Cell viability

The cell counting Kit-8 kit (CCK-8, Beyotime) was used to determine the viability of cells. A 96-well plate containing A549 seeds was incubated at 37°C. After 80–90% of the well is filled with cells, the cells are rinsed with PBS and left in the CCK-8 reagent for 1 hour at 37°C. Using a microplate reader (Infinite F50 Microplate Reader, Switzerland), absorbance was measured at 450 nm.

Measure iron levels

Total iron and Fe^{2+} content in lung tissues and cells were measured using an iron ion assay kit (Sigma-Aldrich) and an iron detection kit (Applygen Technologies, Inc.) according to the kit instructions.

Western blotting

RIPA lysis buffer was used to lyse cells and lung tissue on ice, and the total protein content was determined using the Beyotime bicinchoninic acid (BCA) protein assay kit. Following 12% SDS-PAGE, an equivalent amount of protein extract (30 µg) was transferred to a PVDF membrane (Millipore, Billerica, MA) and blocked with skim milk for an hour. Following primary antibody probing and blotting buffer washing, particular secondary antibodies coupled to horseradish peroxidase were used to incubate the membranes. Using an enzyme-linked chemiluminescence kit (Biological Industries, Kibbutz Beit-Haemek, Israel), the signal was detected. ImageJ software was used to examine blot images. The primary antibody is: N protein (Genscript), ACSL4 (1:1000, ab155282, abcom), GPX4 (1:1000, ab125066, abcom), FTH1 (1:1000, ab75973, abcom), SLC7A11 (1:1000, ab216876, abcom), and GAPDH (ab9485, 1:1000, abcom).

Co-immunoprecipitation (Co-IP)

After precipitating and lysing A549 cells, the BCA technique was used to measure the protein concentration and identify the expression levels of SLC7A11 and N protein. Next, each group received 200 ul of Protein A+G agarose beads; the IP group received SLC7A11 antibody; the IgG group received rabbit IgG; and the groups are bonded for 2 hours at 4°C. Each group received a cell lysis solution, which was then cycled overnight at 4°C. After three PBS washes, SDS loading buffer is added for elution, and the eluent is used for conventional western blotting.

Statistical analysis

A minimum of three independent experiments' mean ± standard deviation (SD) is used to show all data. The Student's *t* test was used to assess the statistical significance of mean differences between the two groups, and one-way analysis of variance (ANOVA) was employed to compare group differences. GraphPad Prism 8.0 was used for statistical analysis. Data were deemed statistically significant when $P < 0.05$.

Results

Recombinant SARS-CoV-2 N protein induces acute lung injury

We evaluated the effect of N protein on lung injury by treating C57BL/6 mice intratracheally with either N protein or PBS. The data demonstrated that N protein treatment caused an inflammatory response, resulting in thicker alveolar septa and more cells. Compared with the control group, the leukocyte infiltration score in the lungs of the N protein group was significantly increased (Figure 1A). Furthermore, when compared to the control group, the levels of the pro-inflammatory cytokines TNF-α, IL-6, and IL-1β were markedly elevated (Figure 1B).

Recombinant SARS-CoV-2 N protein triggers pulmonary ferroptosis

Mice were given either PBS or N protein intratracheally to examine how N protein affected ferroptosis. After 24 hours, lung tissue was taken for analysis. The findings demonstrated that treatment with N protein considerably raised the levels of total iron and Fe^{2+} in lung tissue as compared to the control group (Figure 2A). As is widely known, GPX4 is believed to be essential for preventing ferroptosis. We detected the expression levels of three recognized

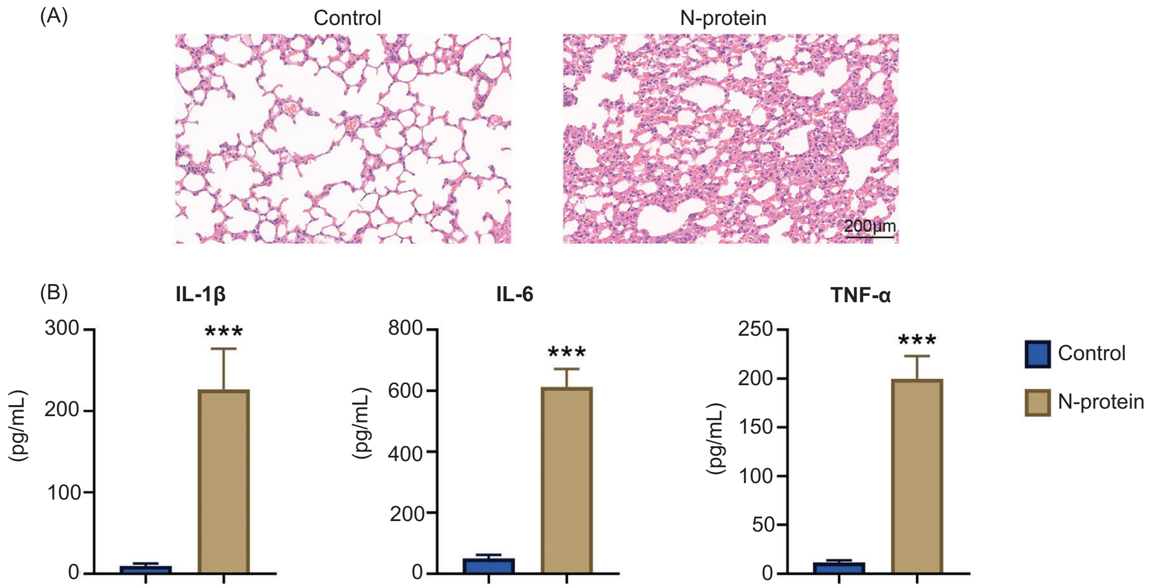

Figure 1 Recombinant SARS-CoV-2 N protein induces acute lung injury. (A) Stain tissue sections with hematoxylin and eosin. Leukocyte infiltration was scored semiquantitatively on a scale from 0 (normal tissue) to 3 (dense filtration). (B) ELISA detects the levels of inflammatory factors IL-1ß, IL-6, and TNF-α in lung tissue. Values are presented as mean ± SD. ***p < 0.001 versus Control group. n=6.

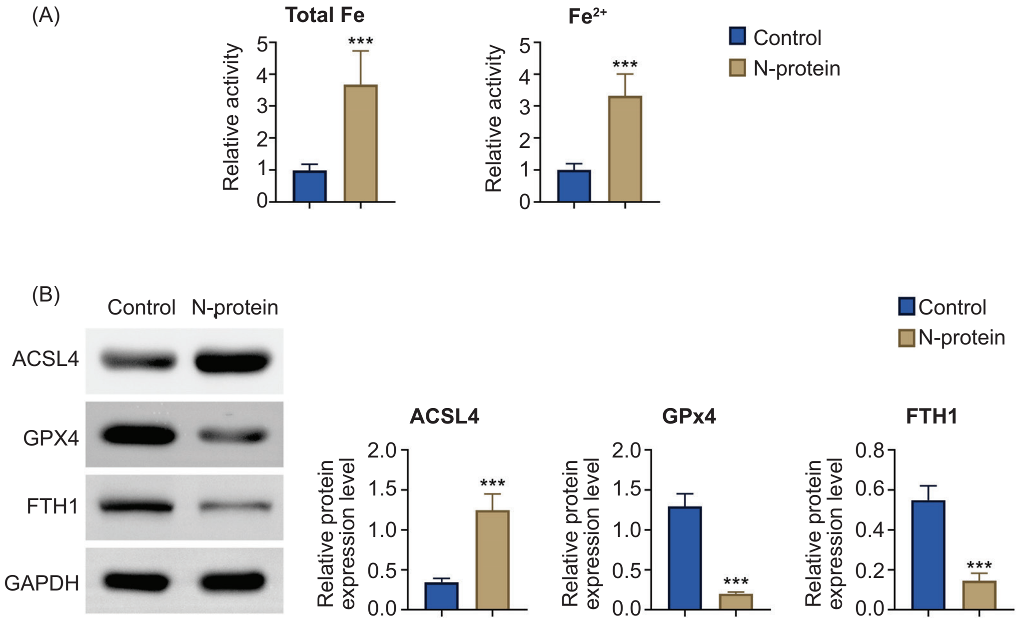

Figure 2 Recombinant SARS-CoV-2 N protein triggers pulmonary ferroptosis. (A) Kit detects total iron and Fe^{2+} content in lung tissue. (B) Western blotting to detect ACSL4, GPX4, and FTH1 protein expression in lung tissue. Values are presented as mean ± SD. ***$p < 0.001$ versus Control group. n=6.

ferroptosis markers, ACSL4, GPX4, and FTH1 in lung tissue. Following treatment with N protein, it was discovered that lung tissue's GPX4 and FITH1 protein expressions dropped but ACSL4 expression increased (Figure 2B).

Recombinant SARS-CoV-2 N protein triggers ferroptosis in lung epithelial cells

In acute lung damage, alveolar epithelial cells are essential. In order to assess the connection between ferroptosis and acute lung injury caused by N protein, we conducted in vitro tests on A549 cells. The results showed that N protein treatment significantly increased the levels of total iron and Fe^{2+} and inhibited cell viability in A549 cells (Figure 3A,B). In addition, after treatment with N protein, it was found that the expression of GPX4 and FITH1 proteins in A549 decreased but the expression of ACSL4 increased (Figure 3B).

Recombinant SARS-CoV-2 N interacts with SLC7A11

We investigated the relationship between N protein and SLC7A11 using Western blotting technology and Co-IP in order to better understand the intrinsic mechanism of N protein influencing ferroptosis in acute lung damage. The findings demonstrate that N protein can bind to SLC7A11 and raise SLC7A11 expression in A549 cells (Figure 4A,B).

Activating SLC7A11 reverses the effects of SARS-CoV-2 N

To further study the mechanism of N protein, we overexpressed SLC7A11. Figure 5A illustrates that SLC7A11 expression was higher in lung tissue as compared to the N protein group, proving that overexpression of SLC7A11 was successful. In vivo experiments and overexpression of SLC7A11 can reverse acute lung injury and ferroptosis caused by N protein (Figure 5B-E). The expression of SLC7A11 was increased in A549 compared with the N protein group, proving that the overexpression of SLC7A11 was successful (Figure 5F). Overexpression of SLC7A11 could reverse N protein-induced ferroptosis in vitro (Figure 5G-I). This proves that N protein causes ferroptosis in acute lung injury through SLC7A11.

Discussion

This study shows that the SARS-CoV-2 N protein causes acute lung injury and ferroptosis in mice by inhibiting SLC7A11. The following results corroborate this conclusion. (1) Recombinant N protein induces lung inflammation in mice. (2) Recombinant N protein induces ferroptosis in vivo and in vitro. (3) Recombinant N protein and SLC7A11 can bind to each other. (4) Activating SLC7A11 reverses N protein-induced acute lung injury and ferroptosis.

Acute lung injury can result from a SARS-CoV-2 infection. One of the main causes is the lung immune system's imbalance, which causes a "cytokine storm" to emerge when a lot of inflammatory chemicals are released.[16] During SARS-CoV-2 infection, dead cells may release substantial amounts of HMGB1 into the extracellular space. As a well-known inflammatory mediator, HMGB1 can trigger the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This cascade of events may impair the function of various immune cells, thereby contributing to uncontrolled viral replication and exacerbating cell damage.[17,18] The innate immune system's key inflammatory

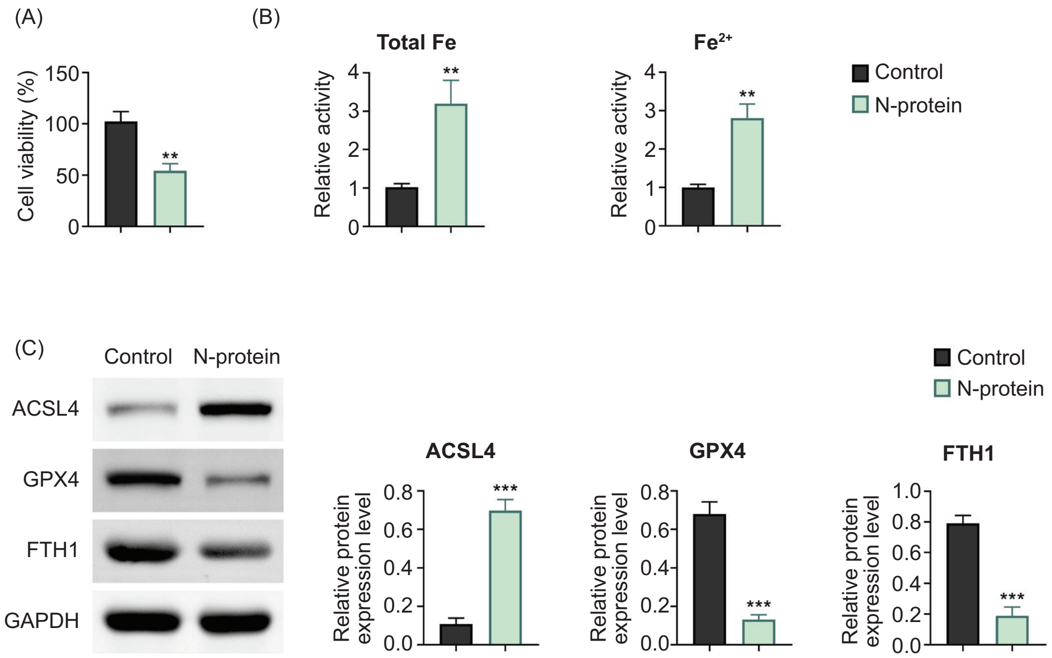

Figure 3 Recombinant SARS-CoV-2 N protein triggers ferroptosis in lung epithelial cells. (A) CCK-8 detects cell viability. (B) Kit detects total iron and Fe2+ content in A549 cells. (C) Western blotting to detect ACSL4, GPX4, FTH1 protein expression in A549 cells. Values are presented as mean ± SD. **p < 0.01, ***p < 0.001 versus Control group. n=3.

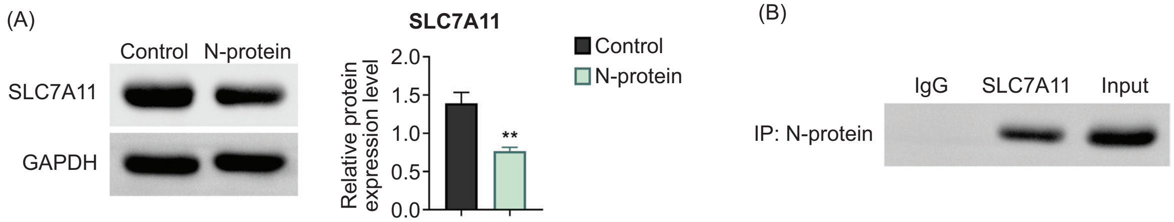

Figure 4 Recombinant SARS-CoV-2 N interacts with SLC7A11. (A) Western blotting to detect SLC7A11 protein expression. (B) Co-immunoprecipitation analysis of SARS-CoV-2 N binding to SLC7A11. Values are presented as mean ± SD. **p < 0.01 versus Control group. n=3.

components, IL-1β, IL-6, and TNF-α, are crucial for the host's protection against viruses.[19] According to clinical research, individuals infected with SARS-CoV-2 have considerably higher levels of IL-1β, IL-6, and TNF-α in their serum and alveolar lavage fluid.[20] N protein causes severe systemic inflammation, according to studies. In addition, within 24 hours of the activation of N protein, cytokine release skyrocketed, causing additional lung tissue injury.[7] Our research results support previous studies that N protein can increase the levels of IL-1β, IL-6, and TNF-α in lung tissue, thereby causing lung damage.

A new kind of iron-dependent programmed cell death is called ferroptosis. It's different from traditional forms of programmed cell death, including autophagy, senescence, necroptosis, and apoptosis.[21] Numerous investigations have revealed a connection between ferroptosis and a number of illnesses, including infections, neurological conditions, and malignancies.[22] Research has indicated a connection between ferroptosis and SARS-CoV-2. For instance, ferroptosis is induced in sinoatrial node pacemaker cells by SARS-CoV-2 infection.[23] The SARS-CoV-2 accessory protein Orf7b causes lung damage by causing ferroptosis and apoptosis mediated by c-Myc.[10] Through receptor-interacting protein kinase 1, the SARS-CoV-2 envelope protein causes necroptosis and promotes inflammatory responses in lung and colon cells.[24] However, the link between SARS-CoV-2 N protein and ferroptosis has been poorly studied. Our data show that N protein can induce ferroptosis in vitro and in vivo.

By transferring extracellular cysteine, SLC7A11, one of the Xc-system's subunits, plays a crucial role in controlling iron overload-ferroptosis.[25] SLC7A11 inhibition decreases cystine absorption, which in turn causes increased intracellular lipid peroxidation and ferroptosis as well as cystine-dependent glutathione peroxidase inactivation.[26] Our findings show that SARS-CoV-2 N protein can bind directly with SLC7A11 and suppress SLC7A11 protein production. Additional research demonstrates that SLC7A11 activation can reverse ferroptosis and acute lung injury brought on by the SARS-CoV-2 N protein. This shows that in acute lung injury, SARS-CoV-2 N interacts with SLC7A11 to induce ferroptosis.

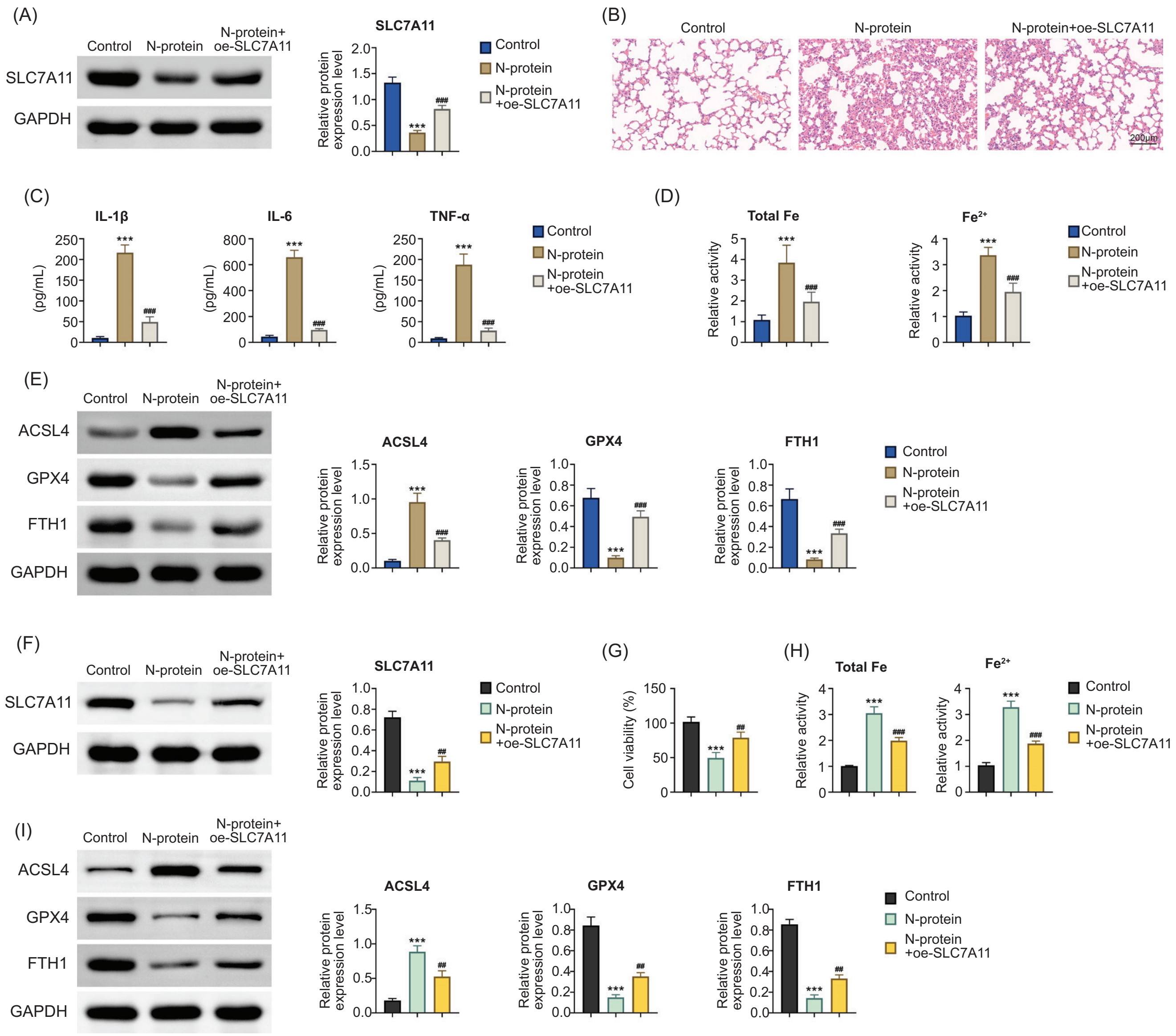

Figure 5 Activation of SLC7A11 reverses ferroptosis in SARS-CoV-2 N-induced acute lung injury. (A) Western blotting to detect SLC7A11 protein expression in lung tissue. (B) Stain tissue sections with hematoxylin and eosin. (C) ELISA detects the levels of inflammatory factors IL-1β, IL-6, and TNF-α in lung tissue. (D) Kit detects total iron and Fe2+ content in lung tissue. (E) Western blotting to detect ACSL4, GPX4, and FTH1 protein expression in lung tissue. (F) Western blotting to detect SLC7A11 protein expression in cells. (G) CCK-8 detects cell viability. (H) Kit detects total iron and Fe2+ content in A549 cells. (I) Western blotting to detect ACSL4, GPX4, and FTH1 protein expression in A549 cells. Values are presented as mean ± SD. ***p < 0.001 versus Control group. $^{\#\#}$p < 0.01, $^{\#\#\#}$p < 0.001 versus N protein group.

Conclusion

In conclusion, our research demonstrates that the SARS-CoV-2 N protein can directly interact with SLC7A11 to cause ferroptosis, which causes the mice to produce a lot of inflammatory factors and develop lung injury. According to our findings, SLC7A11 activation can reduce lung damage brought on by SARS-CoV-2 infection, indicating that SLC7A11 may be a viable target for COVID-19 therapy.

Acknowledgements

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (number: 2021(440)).

Authors Contributions

Conceptualization, methodology, and writing – original draft were performed by Yi Liu; formal analysis, resources, and investigation were performed by Hui Tang; formal analysis, visualization and data curation were performed by Pan Xu; project administration, supervision, and validation were performed by Xiaoqi Zhou; validation, supervision, and writing – review & editing were performed by Shiying Li. All authors read and approved the final manuscript.

Conflicts of Interests

The authors state that there are no conflicts of interest to disclose.

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