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RESEARCH ARTICLE

The role of selenoprotein M in nickel-induced pyroptosis in mice spleen tissue via oxidative stress

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Abstract

Nickel (Ni) is a heavy metal element and a pollutant that threatens the organism's health. Melatonin (Mel) is an antioxidant substance that can be secreted by the organism and has a protective effect against heavy metals. Selenoprotein M (SelM) is a selenoprotein widely distributed of the body, and its role is to protect these tissues from oxidative damage. To study the mechanism of Ni, Mel, and SelM in mouse spleen, 80 $SelM^{+/+}$ wild-type and 80 $SelM^{-/-}$ homozygous mice were divided into 8 groups with 20 mice in each group. The Ni group was intragastric at a concentration of 10 mg/kg, while the Mel group was intragastric at 2 mg/kg. Mice were injected with 0.1 mL/10 g body weight for 21 days. Histopathological and ultrastructural observations showed the changes in Ni, such as the destruction of white and red pulp and the appearance of pyroptosomes. SelM knockout showed more severe injury, while Mel could effectively interfere with Ni-induced spleen toxicity. The results of antioxidant capacity determination showed that Ni could cause oxidative stress in the spleen, and Mel could also effectively reduce oxidative stress. Finally, Ni exposure increased the expression levels of the pyroptotic genes, including apoptosis-associated speck protein (ASC), absent in melanoma-2 (AIM2), NOD-like receptor thermal protein domain-associated protein 3 (NLRP3), Caspase-1, interleukin- (IL-) 18, and IL-1β ($p < 0.05$). Loss of SelM significantly increased these ($p < 0.05$), while Mel decreased the alleviated impact of Ni. In conclusion, the loss of SelM aggravated Ni-induced pyroptosis of the spleen via activating oxidative stress, which was alleviated by Mel, but the effect of Mel was not obvious in the absence of SelM, which reflected the important role of SelM in Ni-induced pyroptosis.

Keywords Nickel · Melatonin · Selenoprotein M · Spleen · Oxidative stress · Pyroptosis

Abbreviations

Ni	Nickel
Mel	Melatonin
SelM	Selenoprotein M
H&E	Hematoxylin-eosin
SOD	Superoxide dismutase
T-AOC	Total antioxidant capacity
MDA	Malondialdehyde
GSSG	Oxidized glutathione disulfide
GSH	Reduced glutathione
qRT-PCR	Quantitative real-time polymerase chain reaction
PMSF	Phenylmethylsulfonyl fluoride
BCA	Bicinchoninic acid
NC	Nitrocellulose
BSA	Bovine serum albumin
LY	Lymphocytes
SP	Spleen cord
SS	Spleen sinus
WP	White pulp
RP	Red pulp
RSC	Red blood cells
ASC	Apoptosis-associated speck protein
AIM2	Absent in melanoma-2
NOX2	Nicotinamide adenine dinucleotide phosphate oxidase 2
NLRP3	NOD-like receptor thermal protein domain-associated protein 3

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TXNIP	Thioredoxin-interacting protein
TRXI	Time-resolved x-ray imager
IL-18	Interleukin- (IL-) 18
PRRs	Pattern recognition receptors
GSDMD	gasdermin D

Introduction

Selenium is a non-metallic element and an indispensable trace element for normal physiological activities of the body (Xue et al. 2022; Zhang et al. 2021a), which is linked to apoptosis (Qing et al. 2022), oxidative stress (Li et al. 2022a), autophagy (Zheng et al. 2021b), and inflammation (Zhang et al. 2021b). The biological function is mainly through the antioxidant effect in the form of selenoprotein and selenozyme, and selenoprotein M (SelM) is one of them (Cai et al. 2022a, b). Moreover, SelM is one of the executive agents of selenium in vivo, which has antioxidant, neuroprotective, and intracellular calcium regulation effects, and distributes widely, especially highly expressed in brain tissue (Chen et al. 2013). Selenoproteins are closely related to body damage caused by toxic substances (Hofstee et al. 2022). A study showed that exposure to mercuric chloride significantly reduced SelM expression in chicken kidneys (Chu et al. 2020). Furthermore, it was confirmed that Se antagonized Pb-induced apoptosis in chicken neural tissue through selenoproteins, including SelM (Zhu et al. 2017).

Nickel (Ni) is a heavy metal widely distributed in the environment, which has become an important pollutant due to the pollution of Ni manufacturing and the burning of fossil fuels. Long-term high-dose exposure has various toxicities to humans and animals. It is a kind of human carcinogen (Guo et al. 2021). Heavy metal poisoning damages immune cells (Xu et al. 2021), especially Ni, and damages the immune system of animals. It was demonstrated that $NiCl_2$ inhibited T-cell function (Harkin et al. 2003). The total number of spleen cells in female mice decreased after 24 h of systemic exposure to Ni (Buxton et al. 2021).

Lead, a heavy metal, can cause oxidative stress in rat nerve tissue (Shaban et al. 2021) and liver (Shaban et al. 2020), and thioacetamide can cause oxidative stress in rat liver (Shaban et al. 2022a). Ni induced increased levels of oxidative stress in rats and inhibited the activities of glutathione peroxidase, catalase, and other antioxidant defense systems in the spleen (Boulila et al. 2014).

Melatonin (Mel) is a hormone secreted by the pineal gland, which has a protective effect on metal toxicity (Romero et al. 2014). Recently, it showed that Mel alleviated the pyroptosis caused by TMT-induced excessive oxidative stress (Cai et al. 2021). At the same time, Mel improved brain autophagy in mice by reducing oxidative stress (Qiao et al. 2022) and improved kidney cell apoptosis in fish by Mir-140-5p/TLR4/NF-κB axis (Li et al. 2022e). However, it has not been reported whether SelM has a role in Ni-induced animal toxicity.

Pyroptosis is a Caspase-11 or Caspase-1-dependent inflammasome-dependent programmed cell death by lysis of cells or, in some cases, by the endosomal sorting complexes required for transport (Du et al. 2021). On the other hand, selenoproteins are closely related to pyroptosis. Thioredoxin reductase 3 is a selenoprotein that inhibits pyroptosis and necrosis (Liu et al. 2022b). Current research has proved that pyroptosis is related to arteriosclerosis (Lin et al. 2022), rheumatoid arthritis (Zhao et al. 2021), diabetic nephropathy (Zuo et al. 2021), central system diseases (Hu et al. 2022), cancer (Al Mamun et al. 2021), and other diseases. Among them, chromium induces pyroptosis of grass carp spleen lymphocytes through oxidative stress and NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) signaling pathway (Zhang et al. 2020). The spleen is an important immune organ in the body. It is the principal place for the production of lymphocytes and the immune response. Studies have confirmed that pyroptosis occurs in the spleen under certain stimuli, and Ni exposure could cause damage to spleen tissue (Boulila et al. 2014; Buxton et al. 2021). However, the role of SelM in Ni exposure-induced spleen pyroptosis was uncertain.

In this study, to explore the role of SelM in the effects of Ni exposure on immune organs in mice and whether Mel could act as a relevant antagonist, we established a SelM knockout mouse model of Ni poisoning and a Mel recovery group model. Our study is aimed at probing the role and mechanism of Ni exposure-induced spleen injury and the antagonism of Mel on Ni through various molecular biology and histomorphological experiments and at clarifying the effect of SelM on Mel antagonism of the Ni-induced spleen in mice tissue pyroptosis. According to the above experiments, it is expected to supply a reference for clinical medication and disease therapy.

Materials and methods

Ethics

All the procedures were approved by the Academic Committee of Northeast Agricultural University.

Mouse model

To construct the model, 160 male C57BL/6 N mice weighing 25–30 g at 8 weeks of age, 80 $SelM^{+/+}$ wild-type, and 80 $SelM^{-/-}$ homozygous mice were randomly divided into 8 groups of 20 mice each, including control, Ni, Mel, Ni + Mel, KO + C, KO + Ni, KO + Mel, and KO + Ni + Mel

groups. SelM$^{-/-}$ homozygous mice were generated by a commercial supplier (Cyagen Biosciences, Santa Clara, CA, USA) using CRISPR/Cas-mediated genome engineering, which is used to design single-guide RNA (sgRNA), and then high-throughput electro-transfer fertilized eggs to obtain SelM$^{-/-}$ homozygous mice. At 9:00 a.m. and 5:00 p.m., the stomach was perfused twice daily with an interval of 8 h, a total of 21 days. The eight groups include control group mice (morning saline, afternoon saline), Ni group mice (morning Ni, afternoon saline), Mel group mice (morning saline, afternoon Mel), Ni + Mel group mice (morning Ni, afternoon Mel), KO + C group mice (morning saline, afternoon saline), KO + Ni group mice (morning Ni, afternoon saline), KO + Mel group mice (morning saline, afternoon Mel), and KO + Ni + Mel group (Ni in the morning, Mel in the afternoon). It is necessary to ensure that each group has the same gastric perfusion time to eliminate the error caused by the gastric perfusion operation. Normal saline (0.9%) is used as the control solution. Ni (Macklin, Shanghai, China) is a 10 mg/kg nickel chloride solution, and the concentration of Mel (Sangon Biotech, Shanghai, China) is 2 mg/kg. Each mouse was given 0.1 mL/10 g body weight by gavage. With regard to Ni and Mel concentrations, according to the previous experiment of the research group and references (Cai et al. 2021; Liu et al. 2022c; Qiao et al. 2022), we selected the minimum concentration of Ni chloride that caused injury to mice and the maximum concentration of Mel that alleviated Ni injury without harming mice. All animals consumed enough food and water for 21 days (Zhang et al. 2022c). The status of mice was observed daily after establishing the model successfully.

Spleen sample collection

The mice were put into clean containers and euthanized by slowly injecting carbon dioxide (CO_2) when the heart and breathing stopped, and the reflex disappeared. After the mice were euthanized, the scalpel and surgical scissors were disinfected. The abdominal cavity was opened, the intestinal tissue was removed, and the spleen was fully exposed and collected. Spleen tissues were harvested for histopathological examination, and remaining spleen tissues were immediately stored at − 80 °C for subsequent experiments (− 80 °C ultra-low temperature preservation box, Haier Company, Qingdao, China) (Chen et al. 2022).

Histological analysis

Fresh spleen tissue was reduced into small 5-μm squares and fixed in a 10% neutral formalin solution (Servicebio, Wuhan, China) for 1 day. The tissues were trimmed, dehydrated, embedded, and sectioned (Xu et al. 2022). These sections were stained with hematoxylin–eosin (H&E), dehydrated, dried, pressed (Zhu et al. 2021), and magnified with a normal optical microscope (Eclipse Ni/Ci, Nikon Eclipse-TI Inc., Tokyo, Japan).

Transmission electron microscopy (TEM)

Spleen samples were left overnight in 2.5% glutaraldehyde and subsequently post-fixed with osmium tetroxide. Afterward, being reduced into thin sections, washed, gradient dehydrated, and resin-soaked, these samples were stained with uranyl acetate (Zhang et al. 2022a). Then, sections were watched and photographed by TEM (JEM-1200ES, JEOL, Tokyo, Japan).

Detection of oxidative stress and antioxidant indicators

Spleen tissues were homogenized in normal sterile saline and centrifuged at 5000 r for 13 min. Next, the supernatant was used (Li et al. 2022b). Several important oxidative and antioxidant indicators were measured by assay kits. Superoxide dismutase (SOD, Jiancheng Bioengineering Institute, Nanjing, China) was determined by the xanthine oxidase method; total antioxidant capacity (T-AOC, Nanjing Jiancheng Bioengineering Institute, Nanjing, China) and malondialdehyde (MDA, Nanjing Jiancheng Bioengineering Institute, Nanjing, China) were determined by the colorimetric method; oxidized glutathione disulfide (GSSG, Geruisi Bio, Suzhou, China) and reduced glutathione (GSH, Geruisi Bio, Suzhou, China) were determined by the spectroscopic method.

RNA isolation and determination of messenger RNA (mRNA) expression of pyroptosis factors

Total RNA was segregated from the spleen using TRIzol reagent (Takara Bio, Dalian, China). Total RNA was synthesized into complementary DNA (cDNA) using superscript II reverse transcriptase (BIOER, Hangzhou, China), depending upon the manufacturer's instructions (Zheng et al. 2021a). The synthesized cDNA was stored at – 80 °C. A quantitative real-time polymerase chain reaction (qRT-PCR) was performed in the LightCyclers@480 II system (FQD-96A, BIOER, Hangzhou, China). Pyroptosis pathway-related genes, such as nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2), apoptosis-associated speck protein (ASC), absent in melanoma-2 (AIM2), NLRP3, Caspase-1, interleukin 18 (IL-18), and interleukin 1-beta (IL-1β), were detected. The housekeeping gene (β-actin) was used as an internal reference (Li et al. 2022c, d; Zhang et al. 2022b). The sequences of the relevant specific primers (Sangon Biotechnology, Shanghai, China) are shown in Table 1.

Table 1 The primers used in the present study

Gene	Serial number	Forward primer (5′-3′)	Reverse primer (5′-3′)
TRX1	AA691155.1	TTCCCTCTGTGACAAGTATTCC	TCAAGCTTTTCCTTGTTAGCAC
TXNIP	NM_023719.2	GTCTTTTGAGGTGGTCTTCAAC	TCACACACTTCCACTATTACCC
ASC	NM_009293.1	ACAATGACTGTGCTTAGAGACA	CACAGCTCCAGACTCTTCTTTA
NLRP3	NM_145827.4	CACCTCTTTGGATATGCTGCC	GAGCGGTATCAGGTTCAGGT
AIM2	NM_001013779.2	AGGAAATTTTTGTGTGTCCATGCT	TACCTTCCATGGGGTGAGGT
Cas1	NM_001379144.1	AGAGGATTTCTTAACGGATGCA	TCACAAGACCAGGCATATTCTT
IL-1β	NM_008361.4	ATTCAGGGACCCTACCCTCTC	GAGGAGATACAACCACAGAG
IL-18	NM_008360.2	ACGATGAAGACCTGGAATC	AACAGTCAGAATCAGGCATA
β-Actin	NM_173979.3	CACTGTCGAGTCGCGTCC	TCATCCATGGCGAACTGGTG

Table 2 The antibodies used in the present study

Antibody name	Dilution ratio	Company information
NLRP3	1:1000	Wanleibio, China
ASC	1:500	Wanleibio, China
Cas1	1:500	Wanleibio, China
IL-1β	1:1500	Wanleibio, China
β-Actin	1:3000	Proteintech, China
Goat anti-mouse IgG	1:1000	Proteintech, China

Protein extraction and Western blot (WB) analysis

The spleen tissue was removed in a 100:1 ratio of RIPA lysate (Biosharp, Beijing, China) and phenylmethylsulfonyl fluoride (PMSF, Biosharp, Beijing, China) and centrifuged at 4 °C for 15 min at 12,000 r/min. The supernatant was aspirated and quantified by bicinchoninic acid (BCA, Mei5bio, Beijing, China). One-fourth of the supernatant volume of sodium dodecyl sulfate (SDS) sample buffer (Biosharp, Beijing, China) was added and boiled for 10 min, followed by protein immunoblot analysis. Prepared sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) gels at 12% and/or 10% concentrations were separated from the proteins by SDS–polyacrylamide gel electrophoresis and transferred to nitrocellulose (NC) membranes at a constant current of 200 mA (Yang et al. 2021). NC membranes were closed with 5% bovine serum albumin (BSA) prepared in TBST for 2 h and incubated with diluted β-actin, ASC, NLRP3, Caspase-1, and IL-1β diluted, respectively. The specific dilution ratio of the antibody (Wanleibio, Shenyang, China) is shown in Table 2 for 12 h at 4 °C. Afterward, the membranes were washed 2–3 times with a test for 15 min each. Subsequently, the membrane was incubated with an anti-rabbit immunoglobulin G (IgG) antibody for 1 h at 37 °C and washed 3 times with TBST for 10–15 min each time. β-Actin content was used as an internal reference. Finally, bands with the chemiluminescence imaging system (Azure Biosystems C300, Azure Biosystems Inc., California, USA) were detected with the ECL kit (Biosharp, Beijing, China).

Statistical analysis

All data were analyzed using GraphPad Prism (GraphPad Software Inc., California, USA) for an unbalanced one-way analysis of variance (ANOVA) combined with Tukey's test (Wu et al. 2022). The data were expressed as the mean ± standard deviation (SD) of triplicate independent experiments. Those with different letters were different from the corresponding groups ($p < 0.05$). Identical letters represented non-significant values ($p > 0.05$).

Results

Loss of SelM aggravated Ni-induced pathological damage, whereas Mel alleviated damage

To observe the effects of Ni and effect of Mel on the action of Nil on wild-type and or Selm knockout mice, histopathological damage by H&E staining for microscopic examination was given in Fig. 1. In the control group, the spleen tissue was neatly arranged. The lymphocytes (LY), spleen cord (SP), and spleen sinus (SS) structures were complete, and the coloration of the white pulp (WP) and the red pulp (RP) was clear. In the Ni group, WP was scattered, and lymphocytes were partially stained. SS was enlarged, and there was slight inflammatory congestion in RP. In the Ni + Mel group, WP was poorly demarcated, and lymphocytes were heavily stained, less severe than those in the Ni group. The KO + C group behaved normally, which was similar to the first group. In the KO + Ni group, WP was scattered; RP was atrophied; SP was broken. There were many red blood cells (RBCs) in the SS, which was aggravated by comparing with the Ni group. In the KO + Ni + Mel group, the WP was atrophied; the lymphocytes were heavily stained; the SS was enlarged. There were a few RBCs in the SS. Mel

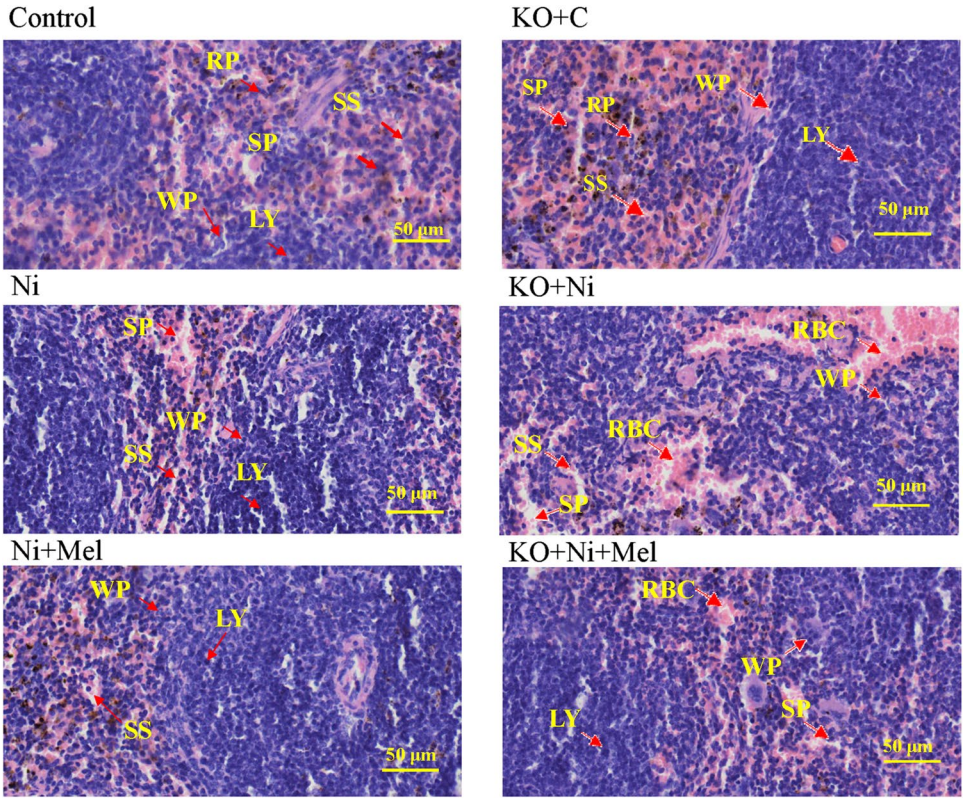

Fig. 1 Effects of nickel, melatonin, and loss of SleM on spleen histology. Red arrows show the specific structure of the spleen, representative photographs of mouse spleens (20 × magnification, scale bar = 50 μm). Abbreviations in the figure are as follows: lymphocytes: LY; spleen cord: SP; spleen sinus: SS; white pulp: WP; red pulp: RP; red blood cells: RSC. Results were expressed as mean ± SD ($n = 20$)

alleviated the pathological damage in the spleen of mice induced by Ni exposure, and SelM knockout aggravated the damage. However, the remission of Mel in the absence of SelM was limited.

The ultrastructure of the spleen was observed by TEM, revealing the effects of Ni on wild-type and SelM gene knockout mice and the effects of Mel on Ni-exposed SelM gene knockout mice in Fig. 2. In the control group, the cells, nuclei, and mitochondria had normal morphology; the nuclear membrane was intact; the nucleoli and mitochondrial cristae were obvious. The chromatin in the Ni group was scattered compared to the previous group. Some mitochondrial cristae were disordered and vacuolated; a few pyroptotic bodies were formed. Compared with the Ni group, the KO + Ni group showed irregular nuclear shape, the disappearance of nucleoli, scattered chromatin in the nucleus, swelling of mitochondria, the disappearance of mitochondrial disorder, partial vacuolization, and a large

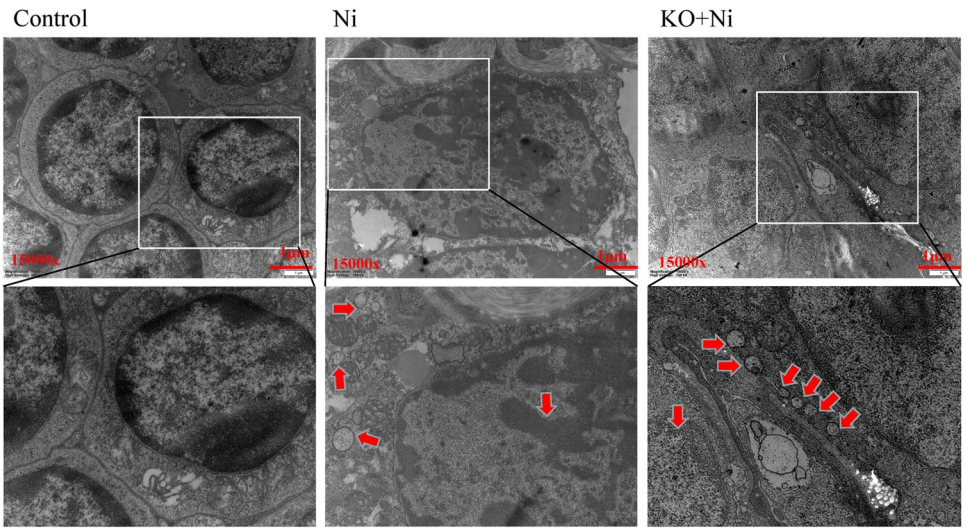

Fig. 2 Effects of nickel, melatonin, and loss of SleM on spleen ultrastructure. Transmission electron microscopy confirmed the changes in the ultrastructure of the spleen, the red arrow only wanted to specify the location of the injury, and the scale bar is 1 μm. Results were expressed as mean ± SD ($n = 20$)

number of pyroptosis bodies. Mel and SelM were protective against spleen injury.

Loss of SelM aggravated Ni-induced changes in oxidative stress parameters, whereas Mel alleviated oxidative stress parameters in the spleen

The levels of oxidative stress markers of antioxidant enzymes (GSH, GSSG, T-AOC, SOD, and MDA) in spleen extracts from treated mice were measured (Fig. 3). As shown in the figure, compared to the previous group, the contents of GSH and GSSG in the Ni group were decreased ($p < 0.05$). In contrast, the activities of T-AOC and SOD were decreased, but the content of MDA was increased, which may explain the inhibitory effect of Ni exposure on antioxidant enzymes in the mouse spleen. Compared with the Ni group, the contents of GSH and GSSG and the activities of T-AOC and SOD in the Ni + Mel group were increased, while the content of MDA was decreased. The results suggested that Mel attenuated the inhibitory effect of Ni exposure on antioxidant enzymes in the spleen of mice. Compared with the Ni group, the contents of GSH and GSSG, as well as the activities of T-AOC and SOD, were significantly decreased in the KO + Ni group, while the contents of MDA were further increased ($p < 0.05$). SelM knockout aggravated the inhibitory effect of Ni-exposure on antioxidant enzymes in the mouse spleen. In contrast, SelM had protective effects on mouse spleen antioxidant enzymes. Simultaneously, compared with the KO + Ni group, the GSH, GSSG contents, T-AOC, and SOD activities in the KO + Ni + Mel group increased, while the MDA contents decreased, but the changes were not enough, which suggests that Mel can alleviate but not counteract the effects of SelM deletion. Thus, these results indicated that Mel alleviated Ni-induced excessive oxidative stress, which was exacerbated by SelM knockout; however, the remission of Mel in the absence of SelM was limited.

Loss of SelM aggravated Ni-induced pyroptosis, whereas Mel alleviated pyroptosis

To test whether the effects of Mel attenuating Ni-exposed spleen toxicity and SelM knockout aggravating Ni-exposed spleen toxicity were associated with pyroptosis, mice were measured by qRT-PCR and WB analysis of pyroptosis genes and proteins in the spleen (Fig. 4). We assessed the pyroptosis in mice spleen by detecting mRNA and protein levels, including ASC, NLRP3, AIM2, Caspase-1, IL-18, IL-1β, and pyroptosis upstream genes, and oxidative stress downstream genes thioredoxin-interacting protein (TXNIP), (time-resolved x-ray imager) TRXI, ASC, NLRP3, Caspase1, AIM2, IL-1β, and IL-18 were increased in the Ni group ($p < 0.05$), showing spleen tissue undergoes pyroptosis, which was compared with the control group. The mRNA levels of pyroptosis-related genes were decreased in the Ni + Mel group compared to the Ni group ($p < 0.05$). Then, the mRNA levels of pyroptosis-related genes were increased in the KO + Ni group compared to the Ni group ($p < 0.05$).

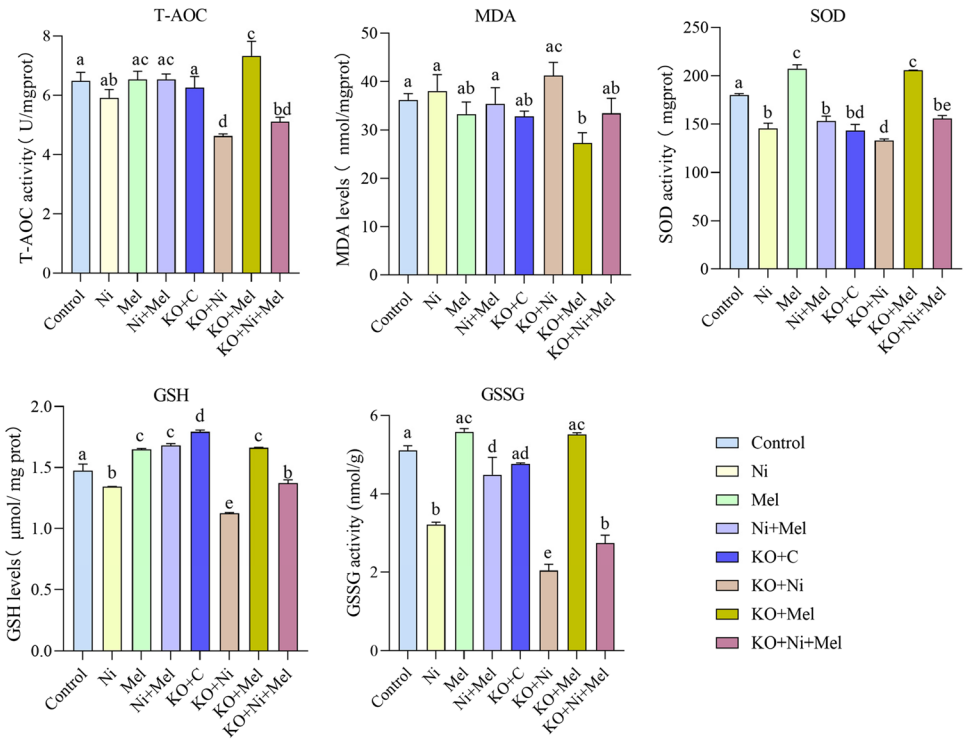

Fig. 3 Effects of nickel, melatonin, and loss of SleM on oxidative stress in the spleen. The contents of MDA, GSH, and GSSG and activities of SOD and T-AOC in the spleen. Different letters represent significant differences ($p < 0.05$), and the same letters represent insignificant differences ($p > 0.05$). Results were expressed as mean ± SD ($n = 20$)

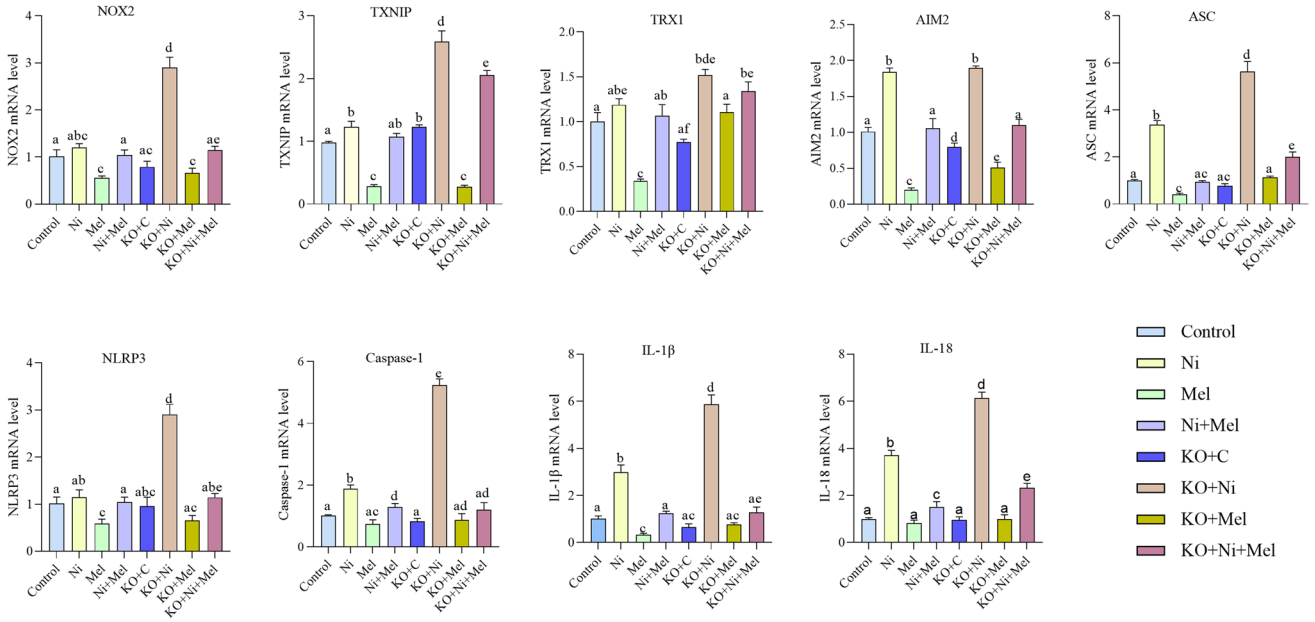

Fig. 4 Effects of Ni, melatonin, and loss of SleM on spleen via TXNIP/NLRP3 pathway. Expression levels of NOX2, TRX1, TXNIP, ASC, NLRP3, AIM2, Caspase-1, IL-18, and IL-1β mRNA in the spleen. Different letters represent significant differences ($p < 0.05$), and the same letters represent insignificant differences ($p > 0.05$). Results were expressed as mean ± SD ($n = 20$)

Furthermore, the levels in the KO + C group were similar to those in the control group. Compared with the KO + Ni group, the KO + Ni + Mel group decreased, but the mRNA levels of pyroptosis-related genes increased compared with the KO + C group ($p < 0.05$).

WB analysis demonstrated the proteins of ASC, NLRP3, Caspase-1, IL-1β, and β-actin, as shown in Fig. 5. Compared with the control group, the protein levels of ASC, NLRP3, Caspase-1, and IL-1β in the spleen of the Ni group, were increased ($p < 0.05$). The protein levels of ASC, NLRP3, Caspase-1, and IL-1β in the spleen were increased in the KO + Ni group ($p < 0.05$) compared to the Ni group. In addition, the levels in the KO + C group were similar to those in the control group. Compared with the KO + Ni group, the

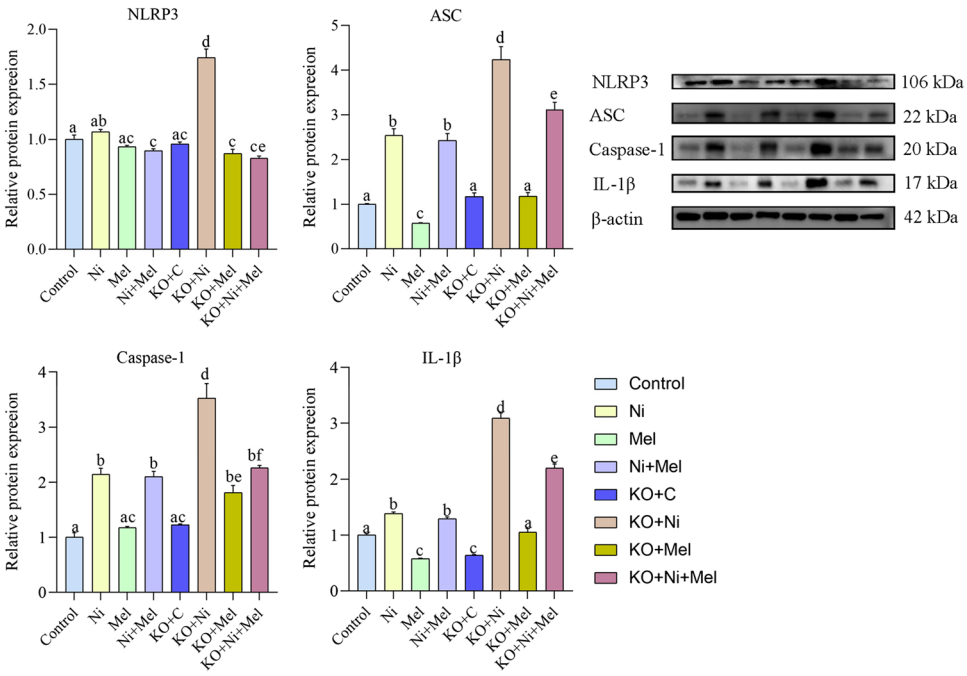

Fig. 5 Effects of Ni, melatonin, and loss of SleM on spleen via TXNIP/NLRP3 pathway. ASC, NLRP3, Caspase-1, and IL-1β protein expression levels in the spleen. Different letters represent significant differences ($p < 0.05$), and the same letters represent insignificant differences ($p > 0.05$). Results were expressed as mean ± SD ($n = 20$)

KO + Ni + Mel group decreased, but ASC, Caspase-1, and IL-1β were more than the KO + C group ($p < 0.05$). Thus, the results suggested Mel attenuated Ni exposure-induced pyroptosis, while SelM knockout exacerbated it; however, the remission of Mel in the absence of SelM was limited (Fig. 6).

Discussion

Ni is a metal that exists in nature and has been extensively used in production, which is a major pollutant. Ni poisoning gets more and more become a public health pollution problem worldwide. At the same time, its exposure may cause cancer, allergic reactions, nephroptosis, hepatotoxicity, neurotoxicity, and immunotoxicity (Guo et al. 2020). Regarding the immunotoxicity of Ni, it is mainly divided into toxicity to non-immune organs and immune organs. Ni decreased the amount of T cells in the intestinal mucosa and the cecal tonsil (Wu et al. 2015). In contrast, Ni reduced the expression levels of spleen TLR4 and TLR7 mRNA, impairing innate spleen immunity (Huang et al. 2014). In addition, Ni had a significant effect on the immune system of the *Carassius auratus*, resulting in a decrease in spleen lymphocytes (Kubrak et al. 2012). Pyroptosis is a novel regulated form of programmed cell death, which is closely related to inflammasome formation (Tsuchiya, 2021). Pyroptosis is related to a variety of diseases, including obstetric diseases (Yu and Li, 2021), liver diseases (Al Mamun et al. 2020), cardiovascular diseases (Wang et al. 2020), and autoimmune system diseases (Wu et al. 2021). Lithium upregulates nuclear factor kappa-light-chain-enhancer of activated B cells (NF/κB) and NLRP3 through reactive oxygen species (ROS), increasing Caspase-3, IL-1β, etc., leading to pyroptosis in mice (Jing et al. 2022). Then, we explored whether Ni could cause spleen pyroptosis in mice. We found that Ni caused spleen tissue damage in mice by H&E staining and pyroptosis by electron microscopy. Oxidative stress can occur in the liver (Shaban et al. 2013) and testis (Shaban et al. 2017). At the same time, oxidative stress can cause apoptosis (Shaban et al. 2022a). In addition, elevated levels of oxidative stress also lead to increased levels of inflammation and fibrosis (Shaban et al. 2022b). In this study, Ni reduced antioxidant capacity and increased oxidative stress in the spleen of mice. Oxidative stress increased levels of pyroptosis-related factors by upregulating TRXI/TXNIP (Song et al. 2021). During pyroptosis, cytoplasmic pattern recognition receptors (PRRs), ASC, and pro-Caspase-1 work together to form activated inflammasomes, which, after cleavage by inflammatory Caspases, release gasdermin D (GSDMD) with perforating activity N-terminal fragment performs pyroptosis, releasing large amounts of IL-1β and IL-18 (Liang et al. 2020). A study showed that chlorpyrifos via miR-124-3p papulosum cyprini cells increased ROS and the occurrence of pyroptosis (Miao et al. 2022). We found elevated levels of TRXI, TXNIP, ASC, NLRP3, AIM2, Caspase-1, IL-1β, and IL-18 ($p < 0.05$) and pyroptosis. To explore the relationship between oxidative stress and Ni-induced pyroptosis, we selected an antioxidant, Mel.

Mel is an indole heterocyclic compound synthesized by unicellular and multicellular organisms from the essential amino acid tryptophan, which is produced in the pineal

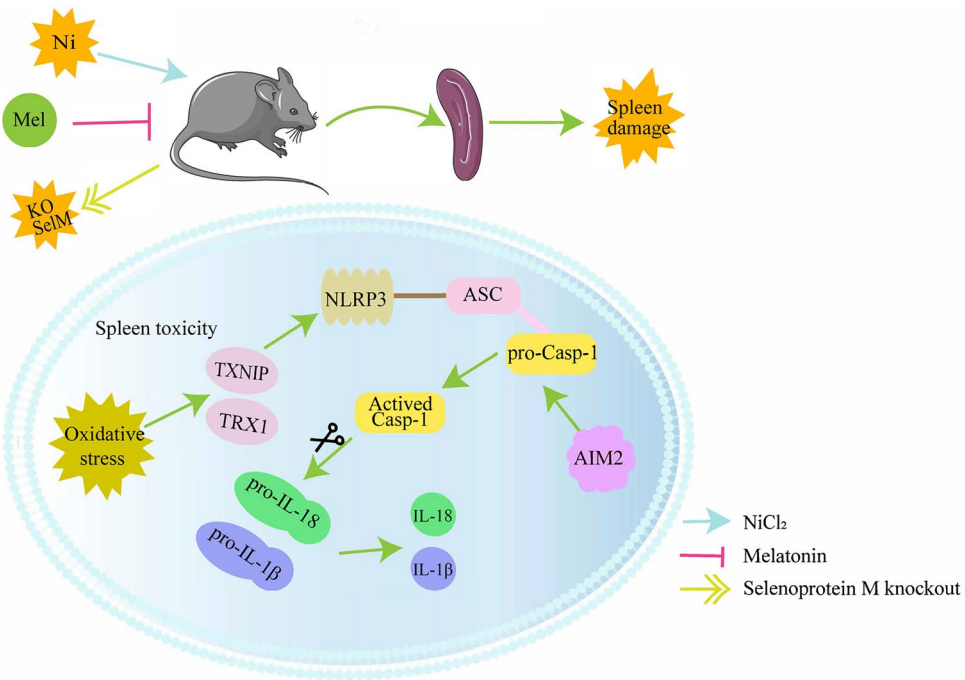

Fig. 6 Schematic representation of the underlying mechanism by which loss of SleM aggravates and melatonin alleviates nickel-induced spleen toxicity. "↓" shows the activation effect and "⊥" shows the suppression effect

gland, kidney, liver, brain, gastrointestinal tract, adrenal glands, and immune system cells (Kvetnoy et al. 2022). It is inextricably linked to the normal function of the body. Mel has been extensively studied due to its potent antioxidant properties in recent years. Mel is associated with treatments for Alzheimer's disease (Park and Kim, 2022), atherosclerosis (Liu et al. 2022a), ischemia–reperfusion (Zhong et al. 2022), osteoarthritis (Zhou et al. 2022), and so on. At the same time, Mel can reduce the damage brought about by poisoning, especially heavy metal poisoning. Mel attenuated aluminum-induced spleen toxicity in mice by inhibiting oxidative stress and the Nrf2 apoptosis signaling pathway (Yu et al. 2019). We found that Mel could alleviate Ni-induced spleen tissue damage in mice by H&E staining and pyroptosis with the electron microscope in mice. However, it is unclear whether Mel could alleviate Ni-induced oxidative stress and pyroptosis in spleen tissue. It was confirmed that Mel could relieve oxidative stress, mitochondrial dysfunction, and apoptosis induced by 2,2,4,4-tetrabromodiphenyl ether (Luan et al. 2022). Regarding the opaque metal Ni related to this study, Mel reduced the oxidative stress caused by Ni and relieved mitochondrial function (Xu et al. 2010). We found that Mel attenuated Ni-induced oxidative stress in the mice spleen; enhanced antioxidant capacity; downregulated TXNIP and TRXI; decreased ASC, NLRP3, AIM2, Caspase-1, IL-1β, and IL-18 ($p < 0.05$); and attenuated pyroptosis. Mel relieves liver fibrosis induced by Txnrd3 knockdown and Ni activation (Liu et al. 2022c). In contrast to the control group, it still showed a damaging effect. Mel alleviated pyroptosis by reducing oxidative stress and improving antioxidant capacity.

We have found that Ni exposure induces spleen pyroptosis in mice, which can be antagonized by Mel. To explore the role of SelM in Mel antagonizing Ni, we performed experiments using SelM knockout mice. Selenoprotein M is a newly discovered selenoprotein with an amino-terminal signal peptide and a thioredoxin-like domain involved in disulfide bond formation and ultimately localizes to the endoplasmic reticulum (Fomenko and Gladyshev 2003). Selenoprotein M is widely distributed, including the cerebral cortex, muscle, liver, and kidney, and protects tissues from oxidative stress (Huang et al. 2016). In addition, there are more and more studies on the effects of selenoproteins, especially SelM, on the body. Selenoprotein M is involved in developing tumors and cancers, including breast cancer and fibrosarcoma (Varlamova et al. 2019). Previous studies have shown that SelM affects the pathogenesis of Alzheimer's disease (Yim et al. 2009). In our previous study, selenoprotein W (SelW) (Yu et al. 2015), selenoprotein T (SelT) (Pan et al. 2018), and selenoprotein S (SelS) (Chi et al. 2021) were closely related to the immune of chickens, including spleen (Khoso et al. 2019), thymus (Khoso et al. 2015a), bursa of Fabricius (Khoso et al. 2015b), trachea (Qin et al. 2020), and neutrophils (Li et al. 2017). However, the role of SelM in Ni-induced pyroptosis of mouse spleen cells has not yet been explored, so we verified this by constructing the SelM knockout model. Through electron microscopy and H&E staining, Ni exposure induced higher pyroptosis levels in the absence of SelM. Wang et al. (2022) found that SelK protected skeletal muscle by reducing endoplasmic reticulum stress and oxidative stress. We found that the KO + Ni group showed more serious spleen damage and higher levels of oxidative stress than the Ni group. Compared with the Ni exposure group, TXNIP and TRXI were upregulated; ASC, NLRP3, AIM2, Caspase-1, IL-18, and IL-1β were increased ($p < 0.05$), elevated levels of pyroptosis. The level of pyroptosis, oxidative stress, and spleen damage in the KO + Ni + Mel group decreased but still showed higher changes compared with the KO + C group. In conclusion, the loss of SelM exacerbated the level of pyroptosis by increasing the degree of oxidative stress. Meanwhile, Mel's mitigation became limited.

Conclusion

Loss of SelM aggravated Ni-induced pyroptosis of the spleen via oxidative stress, but it was alleviated by Mel, which illustrated the protective effect of SelM on mice spleen. Our study is expected to provide a new attempt to treat and study the increasingly serious Ni exposure worldwide and enrich the protective effects of SelM and Mel.

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

Declarations

Ethics approval and consent to participate All the procedures were approved by the Academic Committee of Northeast Agricultural University. They informed and agreed. The approval number is NEAUEC2021 03 22.

Consent for publication All authors have read the manuscript and agreed to submit it in its current form for consideration for publication in the journal.

Competing interests The authors declare no competing interests.

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