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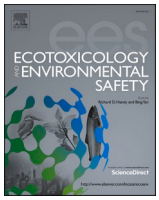

Mitochondrial translation impairment-triggered neuroinflammation mediates fluoride-induced cognitive deficits

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ABSTRACT

Fluoride exposure poses multi-organ toxicity, including skeletal fluorosis, dental fluorosis, neuroinflammation, and cognitive deficits. While fluoride-induced neurotoxicity is linked to mitochondrial dysfunction-particularly via disrupted mitochondrial translation-the mechanistic interplay between translational impairment, neuroinflammation, and cognitive decline remains poorly defined. Here, integrated proteomic and functional analyses revealed that fluoride upregulates mitochondrial ribosomal protein L15 (MRPL15) through its upstream transcription factor CCAAT/enhancer-binding protein-α (C/EBPα) in both *in vivo* and *in vitro* models. This dysregulation perturbed mitochondrial translation fidelity, culminating in mitochondrial reactive oxygen species (mtROS) overproduction. Elevated mtROS activated the NLRP3 inflammasome, triggering pyroptotic cell death and subsequent hippocampal-dependent cognitive impairment. Importantly, the natural compound curcumin (CUR) attenuated fluoride neurotoxicity by enhancing mitochondrial bioenergetics and suppressing the mtROS/NLRP3-pyroptosis axis. Our findings establish mitochondrial translation disruption as a novel mechanism underlying fluoride-induced neuroinflammation and cognitive deficits, urging a critical re-evaluation of fluoride safety thresholds in environmental health policies.

1. Introduction

Fluorine, a ubiquitous inorganic element in natural and biological environments, has seen dramatically increased entry into aquatic systems due to anthropogenic activities including excessive phosphate fertilizer application, coal-fired power generation, brick manufacturing, and industrial processes. This has resulted in persistently elevated fluoride concentrations in groundwater systems (Pickering, 1985). Excessive fluoride intake poses a significant public health challenge globally, with China being one of the most severely affected countries (Wang et al., 2020). Chronic overexposure to fluoride not only induces dental fluorosis and skeletal fluorosis, but also causes multi-organ toxicity affecting the nervous, cardiovascular, and hepatic systems (Chaithra et al., 2020; Solanki et al., 2022). Of particular concern is fluoride's ability to cross both the placental and blood-brain barriers, with additional excretion through breast milk, leading to neurodevelopmental toxicity through accumulation in offspring neural tissues (Qiu et al., 2020; Tian et al., 2020; Yan et al., 2021). Epidemiological evidence demonstrates that prenatal fluoride exposure or residence in high-fluoride areas correlates with significant impairments in learning and memory, along with lower IQ scores compared to their counterparts in low-fluoride regions (Andezhath et al., 1993; Bashash et al., 2017; Choi et al., 2012; Razdan et al., 2017; Zhang et al., 2015). Our previous *in vivo* studies revealed that fluoride exposure induced pathological alterations in rat hippocampal neurons, characterized by increased Nissl body density and mitochondrial abnormalities including swelling and vacuolation. These structural changes were associated with neurodevelopmental deficits and cognitive dysfunction. Furthermore, *in vitro* experiments using rat adrenal pheochromocytoma (PC12) cells demonstrated fluoride-induced mitochondrial disturbances, manifested

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as dysregulated fusion-fission dynamics and impaired translational machinery, ultimately contributing to neuronal dysfunction (Li et al., 2023a; Tian et al., 2024; Zhao et al., 2023).

Mitochondria, the cellular powerhouses, generate adenosine triphosphate (ATP) via the oxidative phosphorylation (OXPHOS) system, which converts energy derived from reducing equivalents (Yousefi et al., 2021). In mammals, the OXPHOS system comprises five multimeric protein complexes (Complexes I-V). Due to the dual genetic control of mitochondria, OXPHOS assembly requires coordinated contributions from both nuclear and mitochondrial genomes: the majority of OXPHOS subunits and ancillary proteins are encoded by nuclear DNA (nDNA), translated by cytosolic ribosomes, and imported into mitochondria, whereas 13 core subunits are directly synthesized via mitochondrial DNA (mtDNA)-dependent replication, transcription, and translation (Kummer and Ban, 2021). The precise stoichiometric assembly of these complexes critically depends on balanced expression between nDNA- and mtDNA-encoded subunits. Dysregulation of this process—whether through impaired replication, transcription, or translation—induces proteotoxic stress and excessive mitochondrial reactive oxygen species (mtROS) production (Soto et al., 2022). Notably, mitochondrial translation defects disrupt the formation of core OXPHOS subunits, thereby compromising nuclear genome-driven respiratory chain function. This cascade leads to ATP depletion, pathological mtROS accumulation, and multisystem disorders (Boczonadi and Horvath, 2014; Hughes et al., 2024). For instance, deficiency in mitochondrial translation elongation factor EF4 causes Complex IV dysfunction, resulting in mtROS overproduction implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's (Li and Qin, 2018). Similarly, loss-of-function mutations in COX14, a mitochondrial translation regulator, trigger excessive mtROS generation and hepatic inflammation in mice (Aich et al., 2024). Consistent with these findings, our prior studies demonstrated that fluoride-induced neurodevelopmental toxicity is associated with mitochondrial translational dysfunction (Li et al., 2023a). Collectively, these data suggest that fluoride may provoke neuronal damage by disrupting mitochondrial translation machinery and subsequent mtROS overproduction, although the precise mechanistic pathways remain to be elucidated.

Mitochondrial translation is a complex process essential for the synthesis of proteins encoded by mtDNA. This process requires the coordinated involvement of numerous factors, including nuclear-encoded mitochondrial ribosomal proteins (MRPs), mitochondrial translation factors, mtDNA-encoded components, aminoacyl- transfer RNA (tRNA) synthetases, and assembly factors (Kehrein et al., 2013). MRPs form the structural core of the mitochondrial ribosome and are crucial for its assembly and stability. Mitochondrial translation factors regulate the four key steps: initiation, elongation, termination, and ribosome recycling(Greber et al., 2014). The mtDNA-encoded components refer to the 13 core subunits of the OXPHOS system; abnormalities in these components can impair respiratory chain function, leading to disruptions in ATP production, mtROS homeostasis, and multi-system disorders (Boczonadi and Horvath, 2014; Hughes et al., 2024). Aminoacyl-tRNA synthetases and assembly factors contribute to the fidelity of protein synthesis (Sissler et al., 2017) and the correct assembly of mitochondrial ribosomal subunits (Tang et al., 2020), respectively, thereby maintaining normal mitochondrial translation. Among these, MRPs regulate mitochondrial translation function through multiple dimensions. MRPs are synthesized in the cytoplasm and transported into mitochondria to facilitate ribosome assembly (Bacon et al., 2024). The mitochondrial ribosome serves as the physical foundation for translation and is involved in processes such as protein synthesis, processing, and folding (Kogure et al., 2014; Richter et al., 2010), thereby sustaining normal mitochondrial function. Like other ribosomes, the mitochondrial ribosome consists of two functionally distinct subunits. The small 28S subunit facilitates the interaction between mRNA and tRNA and helps coordinate the rate of mitochondrial gene expression. The large 39S subunit catalyzes peptide bond formation, ensuring the accuracy and efficiency of translation (Greber and Ban, 2016; Lopez Sanchez et al., 2021). Studies have shown that abnormalities in mitochondrial ribosomal proteins are associated with various neurological disorders, including Parkinson's disease, cerebellar atrophy, and intellectual disability (Li et al., 2018; Lopez Sanchez et al., 2021). Multiple studies have reported that MRPL15, a component of the large ribosomal subunit, is implicated in several diseases, including Alzheimer's disease (AD) (Desai et al., 2020; Peng et al., 2021). Furthermore, MRPL15 has been identified as a potential mitochondrial biomarker and prognostic indicator for the development and metastasis of various cancers (Sotgia et al., 2017; Xu et al., 2021; Zeng et al., 2021). In addition, our proteomic analysis of hippocampal tissues from fluoride-exposed rats revealed that NaF upregulates the expression of MRPL15. However, it remains unclear whether MRPL15 is involved in fluoride-induced neurotoxicity and through which mechanisms it may contribute to its progression.

Pyroptosis is a form of cell inflammatory death triggered by inflammasomes (Kovacs and Miao, 2017), including the classical pathway dependent on cysteine-requiring aspartate protease 1 (Caspase-1) and pathways dependent on other cysteine aspartate proteases. In the classical pathway of pyroptosis, the assembly of NLR family pyrin domain-containing protein 3 (NLRP3), apoptosis-associated speck-like protein containing a CARD (ASC), and caspase-1 forms the NLRP3 inflammasome. After activation by the NLRP3 inflammasome, Caspase-1 cleaves gasdermin D (GSDMD) and interleukin-1β (IL-1β) precursors. Cleaved GSDMD can form pores on the cell membrane, leading to the release of activated IL-1β and other inflammatory factors, triggering cell inflammatory death (Jia et al., 2019).Pyroptosis is widely involved in the occurrence of diseases such as cancer (Liu et al., 2024b), neurodegenerative disorders (De Virgilio et al., 2016; Oladapo et al., 2024), and gastrointestinal diseases (Selim et al., 2023; Sun et al., 2021). The NLRP3 inflammasome is a key trigger factor of the classical pyroptosis pathway (Zhaolin et al., 2019), and suppressing the synthesis of the NLRP3 inflammasome significantly alleviates the cognitive impairment caused by neuroinflammation (Que et al., 2020). Research has shown that excessive activation of NLRP3 exacerbates pathological changes in neurological diseases such as Parkinson's disease (PD) and (AD), leading to a decline in cognitive and behavioral abilities (Li et al., 2023b; Panicker et al., 2022). Inhibiting the activation of the NLRP3 inflammasome can improve the memory and cognitive abilities of diabetic mice (Zhang et al., 2022). The activation of the NLRP3 inflammasome is influenced by various complex factors, most of which are related to the abnormal accumulation of mtROS. MtROS have been shown to promote pyroptosis (Kovacs and Miao, 2017). ROS generation is a potent inducer of NLRP3 inflammasome assembly and activation, whereas pharmacological or genetic inhibition of ROS suppresses this process (Gurung et al., 2015). Notably, mtROS activate the NLRP3 inflammasome not only directly but also through indirect mechanisms involving thioredoxin-interacting protein (TXNIP)-mediated interactions and cytosolic release of mtDNA, which serves as a damage-associated molecular pattern (DAMP) (Zhou et al., 2011). These activation cascades ultimately culminate in context-dependent neuronal injury and cognitive deficits (Xi et al., 2016; Zhang et al., 2023). However, the potential involvement of mtROS-driven pyroptosis in the pathogenic mechanisms underlying fluoride-induced neurotoxicity remains to be further elucidated.

Curcumin (CUR), a natural plant polyphenol, can prevent the occurrence of certain nervous system diseases owing to its excellent anti-inflammatory and antioxidant properties (Liu et al., 2018). Clinical studies have consistently demonstrated that CUR can reduce the risk of depression, schizophrenia, and other neurological illnesses (Patel et al., 2020). Mishra reported that CUR treatment can reduce ROS levels in primary hippocampal neurons, hindering neuronal apoptosis (Mishra et al., 2011). CUR can reverse the excessive generation of ROS induced by α-synuclein in SH-SY5Y and PC12 cells, protecting neurons from oxidative stress damage (Liu et al., 2011). Additionally, Gasmi A et al. reported that ROS generated in cells due to external stimuli can be

cleared by CUR, restoring normal cellular conditions (Gasmi et al., 2022). In this study, we used CUR to reduce the excessive generation of mtROS to prevent pyroptosis and protect neurons from the fluoride-related injury.

Consequently, our study aimed to clarify the role of disordered mitochondrial translation in pyroptosis both *in vivo* and *in vitro*, with the goals of revealing the mechanism of toxicity and identifying potential targets of fluoride. Additionally, we explored the prevention of fluorosis by CUR and proposed innovative public health measures to address endemic fluorosis.

2. Materials and methods

2.1. Cell culture and treatments

Rat pheochromocytoma cells (PC12), acquired from the Academy of Sciences in China, were cultivated in RPMI 1640 medium (Gibco) supplemented with 10 % (v/v) fetal bovine serum (Gibco, Life Technologies, Australia) under conditions of 5 % CO_2 and 37℃. To prepare a stock solution with a concentration of 4 g/L, NaF was dissolved in double-distilled water (dd-H_2O) and then sterilized via a 0.22 μm filter from Merck Millipore (Ireland). CUR (purity > 99 %, CS-1490), dissolved in dimethyl sulfoxide (DMSO), was prepared as a stock solution with a concentration of 50 mmol/L.

Experiment 1. NaF dose exposure treatment

When cell density reached 80 %, the original culture medium was removed and replaced with NaF working solutions, which were prepared by diluting the stock solution with RPMI 1640 medium to concentrations of 20, 40, or 80 mg/L. Following 24 h of incubation, the cells were collected for subsequent processing.

Experiment 2. Combined treatment with gene silencing and NaF

Lipofectamine 3000 co-transfection reagent, negative control (NC) siRNA, C/EBPα-siRNA and MRPL15-siRNA were dissolved in Opti-MEM. After standing for 5 min, NC-siRNA, C/EBPα-siRNA and MRPL15-siRNA were mixed with the co-transfection reagent and then added to the Petri dish after standing for 15 min. Following a 6 h incubation, the medium was removed, and the complete medium was replenished for another 24 h. Subsequently, the medium was discarded, and the cells were treated with 80 mg/L NaF for an additional 24 h.

Experiment 3. Combined treatment with CUR and NaF

PC12 cells were cultured in four 6 cm dishes until reaching suitable density. Two dishes were treated with 10 μmol/L CUR, while the remaining two dishes received complete medium containing an equivalent amount of DMSO as control. After 24 h of treatment, the original medium was discarded. Then, 80 mg/L NaF was added to one of the CUR-treated culture systems and one of the complete medium-treated culture systems respectively. Following another 24 h incubation, cells were collected for subsequent processing.

2.2. Western blotting

IP lysis buffer (Beyotime Institute of Biotechnology, China) was used to extract proteins from cells, which were quantified with BCA protein assay kits. These isolated proteins were separated on SDS—PAGE gels at concentrations of either 10 % or 12 % and subsequently transferred onto PVDF membranes manufactured by Roche, Inc., USA. A blocking step was carried out using 5 % skim milk at room temperature for 2 h. Subsequently, the membranes were incubated with primary antibodies (NLRP3 1:1000, Abclone; GSDMD/N-GSDMD 1:500, HuaBio; Caspase-1/cleaved Caspase-1 1:500, HuaBio; pro IL-1β/IL-1β 1:500, Affinity; C/EBPα 1:2000, Proteintech; MRPL15 1:2000, Proteintech; MT-ND5 1:2000, Proteintech; MT-ATP6 1:2000, Proteintech; MT-CYB 1:2000, Proteintech; MT-CO2 1:1000, Proteintech; mtRF1L 1:1000, Proteintech; mtEFTu 1:2000, Proteintech; MRRF 1:1000, Proteintech; mtIF3 1:1000, Proteintech, and GAPDH 1:4000, Bioworld; at 4℃ overnight (12–16 h), followed by a 1 h incubation with secondary antibodies at room temperature.

2.3. Immunofluorescence

After being treated with 4 % paraformaldehyde, the cells were permeabilized with Triton X-100 for 30 min and then incubated with 10 % goat serum (diluted in PBS). After that, primary antibody against N-GSDMD was added, and the samples were incubated at 4°C overnight. On the second day, Alexa Fluor 594 red fluorescence was used to label the cells with goat anti-rabbit IgG (1:400), and the samples were incubated at room temperature for 1.5 h. Finally, the cells were stained with DAPI for 15 min and observed under an EVOSTM M7000 inverted fluorescence microscope.

2.4. Flow cytometry

Experiment 1. Mitochondrial membrane potential (MMP)

After exposure and intervention, the PC12 cells were digested with trypsin and transferred to EP tubes. After being resuspended in PBS, the cells were treated with JC-1 for 25 min and resuspended in PBS before being transferred to a dedicated flow tube. Tests were conducted via an Attune NxT flow cytometer, and the results were analyzed via Attune NxT software. The experiment mixture was shielded from light after the addition of JC-1 until the end of the assay.

Experiment 2. MtROS

After trypsin digestion, the PC12 cells were resuspended in a single-cell suspension in PBS. Subsequently, MitoSOX RED (Thermo, M36009, China) was added, and the mixture was incubated for 20 min and resuspended in PBS before being transferred to a dedicated flow tube. Tests were conducted via an Attune NxT flow cytometer, and the results were analyzed via Attune NxT software. The experiment mixture was shielded from light after the addition of MitoSOX RED until the end of the assay.

2.5. Cell viability assay

Cell viability was measured via a cell counting kit-8 (CCK-8) assay. When the density of PC12 cells in 96-well plates reached 80 %, they were treated with siRNA or CUR and exposed to NaF. After treatment, 20 μL of a 1:1 mixture of CCK-8 and 1640 medium was added to each well and incubated at 37°C for 50–60 min. Absorbance was measured at 450 nM via a microplate reader (HITACHI, Tokyo, Japan).

2.6. Animals and treatments

Eight-week-old female and male Sprague-Dawley (SD) rats were housed in an SPF animal room under controlled conditions (22–26℃, 50 %-60 % RH, 12-hour light/dark cycle). After a week of acclimation, the female rats were randomly assigned to four groups: the control (natural water <1 mg/L fluoride) and three sodium fluoride (NaF) exposure groups (10, 50, and 100 mg/L NaF). After 30 days, exposed females were paired 2:1 with unexposed males. Pregnant females were housed separately, and their respective NaF exposures were continued. Birth was designated postnatal day 0 (PND 0), and offspring were exposed to the same NaF concentrations as their mothers until PND 60. Animals were sourced from the Hubei CDC's Experimental Animal Research Center, and studies were approved by Huazhong University of Science and Technology's Animal Care and Use Committee.

2.7. Morris water maze (MWM) test

From each group, five male rats were chosen for assessment of learning and memory. The pool, which was divided into four quadrants by an imaging system, featured a platform in the third quadrant. The five-day experiment included four days of navigation tests, during which the rats swam from fixed points for 60 s or until they found the platform. After each test, the samples were allowed to rest on the platform for 20 s. On the fifth day, a spatial probe test was conducted without the platform, following the same procedures. Swimming latency, distance, and platform crossings, automatically recorded by the system, served as evaluation criteria.

2.8. Proteomic analysis of the rat hippocampus

Three rats from both the control group and the 100 mg/L NaF group were randomly selected for hippocampus isolation for proteomic sequencing. Protein concentrations were measured via the Bradford method with modifications, followed by isotope labeling via iTRAQ. NanoLC—MS/MS analysis was carried out on a nanoflow HPLC system. The raw mass spectrometry data were processed via the Sequest module and analyzed with ProteomeDiscoverer 1.3, ensuring a false discovery rate of less than 1 % for peptide matches. Proteins showing fold changes greater than 1.20 and a P value of less than 0.05 were considered differentially expressed (DEPs). The functional enrichment analysis of the GO terms was conducted via DAVID 6.8, and the hypergeometric test was applied to identify DEP enrichment among the identified proteins.

2.9. Statistics

The experimental data were analyzed via SPSS 24.0 (IBM SPSS Inc., USA) and are presented as the means ± S.D.s. One-way ANOVA was conducted to test differences among groups, with subsequent application of the least significant difference (LSD) test. A $P < 0.05$ indicated a statistically significant difference.

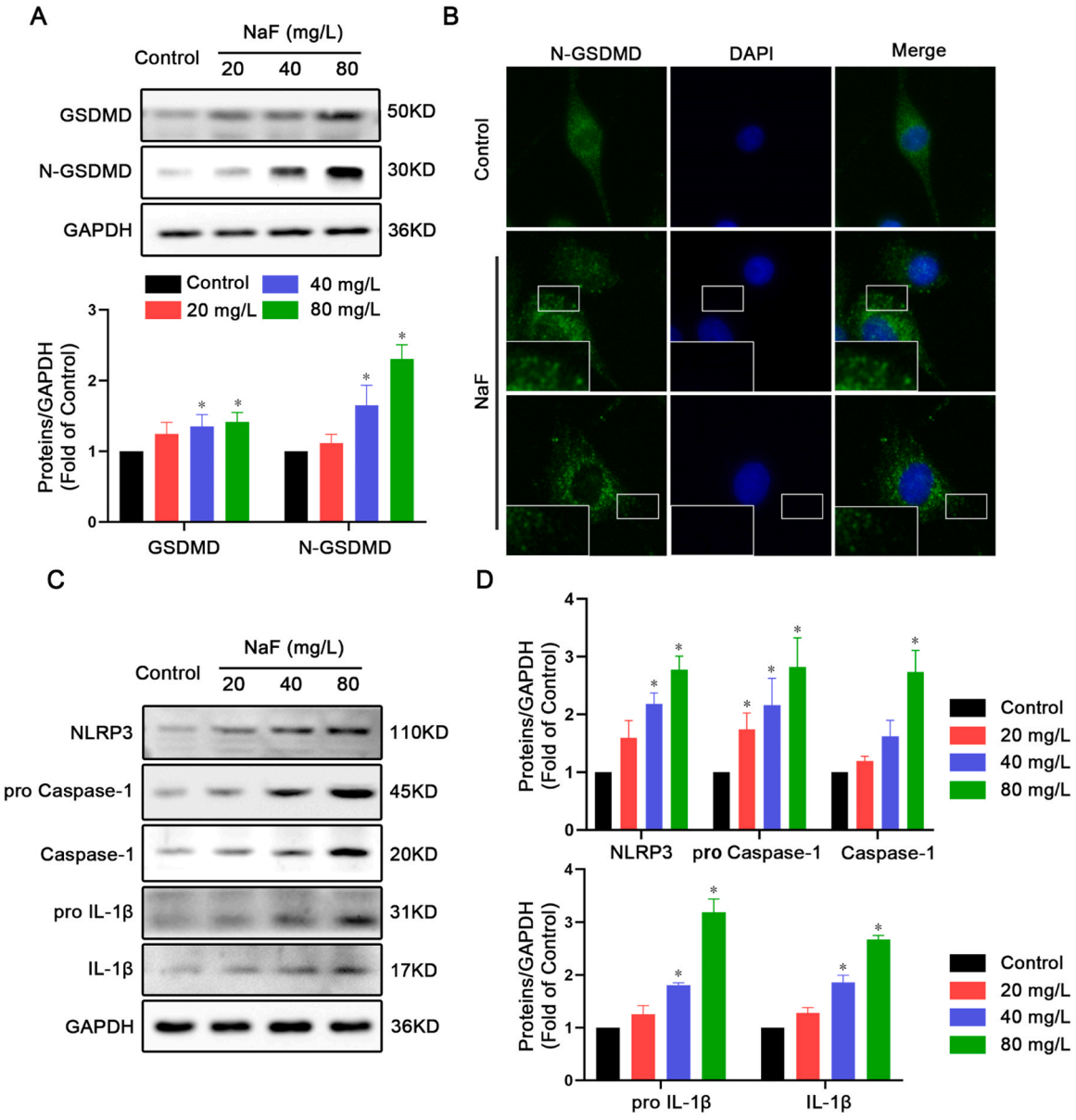

Fig. 1. Fluoride activated NLRP3/Caspase-1 signaling pathway-mediated pyroptosis in PC12 cells. PC12 cells were treated with 0, 20, 40, or 80 mg/L NaF for 24 h. (A, C, D) Western blot analysis of pyroptosis-related protein expression levels, with GAPDH used as a control. (B) Representative images showing N-GSDMD localization (green) in PC12 cells stained with DAPI (blue), 40X. The data are presented as the means ± S.D.s of triplicate samples; *$P < 0.05$ vs. the control.

3. Results

3.1. Fluoride leads to the NLRP3/Caspase-1 signaling pathway of pyroptosis in PC12 cells

As shown in Fig. 1A and B, 24-hour NaF exposure significantly upregulated the expression of GSDMD and its cleaved form N-GSDMD, accompanied by N-GSDMD-mediated pore formation on cell membranes. Fig. 1C and D further revealed that NaF treatment induced a dose-dependent increase in the expression levels of NLRP3, pro-Caspase-1/Caspase-1, and pro-IL-1β/IL-1β compared to the control group. These findings demonstrate that fluoride activates the NLRP3/Caspase-1 pyroptotic signaling axis, contributing to neuronal injury through environmental toxicant-driven inflammatory cascade.

3.2. Fluoride upregulates MRPL15 expression through C/EBPα in PC12 cells

Proteomic results suggested that fluoride may affect the expression of the MRPL15, which is closely related to mitochondrial translation (Fig. 2A, B). Consistently, we observed that NaF exposure upregulated the expression of MRPL15 and its upstream transcription factor, C/EBPα, in PC12 cells (Fig. 2C). These results prompted us to further investigate the role of the C/EBPα/MRPL15 axis in fluoride-induced mitochondrial translation impairment through subsequent knockdown experiments targeting both MRPL15 and C/EBPα.

To verify whether NaF affects the expression of MRPL15 through the transcription factor C/EBPα, we knocked down C/EBPα using C/EBPα-siRNA and detected both the protein and mRNA expression levels of MRPL15. The results indicated that NaF indirectly elevated MRPL15 expression by upregulating C/EBPα (Fig. 2E).

3.3. Knockdown of C/EBPα and MRPL15 activates mitochondrial translation to counteract fluoride-induced mitochondrial dysfunction in PC12 cells

MRPL15, a mitochondrial ribosomal protein, plays a critical role in mitochondrial translation. To validate its involvement in fluoride-induced mitochondrial translational dysfunction, we knocked down MRPL15 expression in PC12 cells using siRNA. As shown in Fig. 3, MRPL15 silencing partially restored the expression of mitochondrial translation-related factors compared to the NaF-exposed group, subsequently upregulating the synthesis of mitochondrial translation products. Further, knockdown of C/EBPα, an upstream regulator of MRPL15, similarly increased the expression of mitochondrial translation factors and their encoded polypeptides (Fig. 4). Combined with Fig. 2, these findings demonstrate that NaF triggers mitochondrial translational impairment by upregulating MRPL15 via C/EBPα.

3.4. Knockdown of C/EBPα and MRPL15 reduces the occurrence of pyroptosis to reverse the neurotoxicity of fluoride in PC12 cells

Fluoride exposure induced MMP disruption in PC12 cells. To investigate the underlying mechanisms, we performed in vitro knockdown of C/EBPα and MRPL15 using siRNA. Compared to the NaF-treated group, silencing C/EBPα and MRPL15 significantly restored MMP stability (Fig. 5A). Subsequent MitoSOX Red staining revealed a marked increase in mtROS levels in NaF-exposed PC12 cells, which was effectively attenuated by C/EBPα and MRPL15 knockdown (Fig. 5B). These results collectively demonstrate that targeting C/EBPα and MRPL15 mitigates NaF-induced mtROS overproduction, thereby protecting PC12 cells from fluoride-mediated mitochondrial oxidative damage.

To elucidate the role of mitochondrial translation in fluoride-induced pyroptosis, we employed MRPL15-siRNA and C/EBPα-siRNA to knock down their expression in an in vitro model. As shown in, MRPL15 knockdown significantly attenuated fluoride-triggered upregulation of pyroptosis-associated proteins (Fig. 6A, B). Furthermore, C/EBPα silencing reduced pyroptosis and subsequent inflammatory responses by modulating MRPL15 expression (Fig. 6C, D). These findings collectively demonstrate that mitigating mitochondrial translational dysfunction and mtROS accumulation suppresses pyroptotic activation and downstream inflammatory cascades.

3.5. CUR antagonizes fluoride neurotoxicity by reducing mtROS-mediated pyroptosis in PC12 cells

Compared to the NaF-treated group, the NaF + CUR co-treatment group exhibited significant improvements in restoring MMP and suppressing mtROS accumulation (Fig. 7A, B). CUR treatment markedly reduced the expression levels of GSDMD and its cleaved form N-GSDMD, indicating alleviation of fluoride-induced pyroptotic cell membrane damage (Fig. 7C). Furthermore, the expression levels of pyroptosis-associated proteins were significantly downregulated (Fig. 7D). These findings collectively demonstrate that CUR mitigates fluoride neurotoxicity by inhibiting the mtROS-mediated pyroptosis pathway.

3.6. Fluoride leads to the classical pathway of pyroptosis in the hippocampus of SD rats

The results of the MWM experiment revealed that NaF exposure in SD rats led to significant impairments in learning and cognitive abilities. Specifically, it increased the swimming distance and latency time required by the rats to navigate the maze.

Compared with those of the lower groups, the time spent swimming in the quadrant with the platform and the frequency of crossing the platform position of the high-dose NaF exposure group were significantly lower (Fig. 8). Collectively, these data showed that NaF can induce memory deficits in rats.

Moreover, our study revealed an increase in the expression levels of proteins associated with C/EBPα-MRPL15 and pyroptosis in the hippocampus of rats exposed to fluoride. This, in turn, negatively affects the learning and cognitive capacities of rats.

4. Discussion

This study explored the neurotoxic mechanisms of fluoride. We found that fluoride interferes with mitochondrial translation and induces neuronal pyroptosis, suggesting a potential link to fluoride-induced cognitive impairment. Proteomic analysis of mitochondrial proteins in fluoride-exposed rats revealed elevated expression of MRPL15 and C/EBPα, which was also confirmed in fluoride-exposed cells. MRPL15 is a mitochondrial ribosomal protein essential for protein synthesis (Gao et al., 2021), and it is associated with neurological disorders caused by mitochondrial dysfunction (Huang et al., 2014). Our research confirmed that elevated expression of MRPL15 disrupts the standard process of mitochondrial translation, thereby compromising normal mitochondrial function. C/EBPα binds to the promoter region of the MRPL15 gene, repressing its expression and thereby impairing mitochondrial translation, which ultimately triggers the accumulation of mtROS. Excessive production or accumulation of mtROS triggers pyroptosis, ultimately driving neuroinflammation. Silencing C/EBPα and MRPL15 attenuates fluoride-induced mtROS accumulation, thereby suppressing NLRP3 inflammasome activation and mitigating fluoride-triggered pyroptosis, which demonstrates that the C/EBPα-MRPL15-mtROS axis contributes to the neurotoxicity of fluoride via pyroptotic pathways.

MRPL15, a core component of the mitochondrial ribosome large subunit (39S subunit), is localized within the mitochondrial matrix and stabilizes ribosomal architecture through interactions with MRPL13 and MRPL19 (Brown et al., 2014). Its primary role involves translating mtDNA-encoded subunits of OXPHOS complexes (e.g., COX1, ND4), thereby directly regulating respiratory chain assembly efficiency

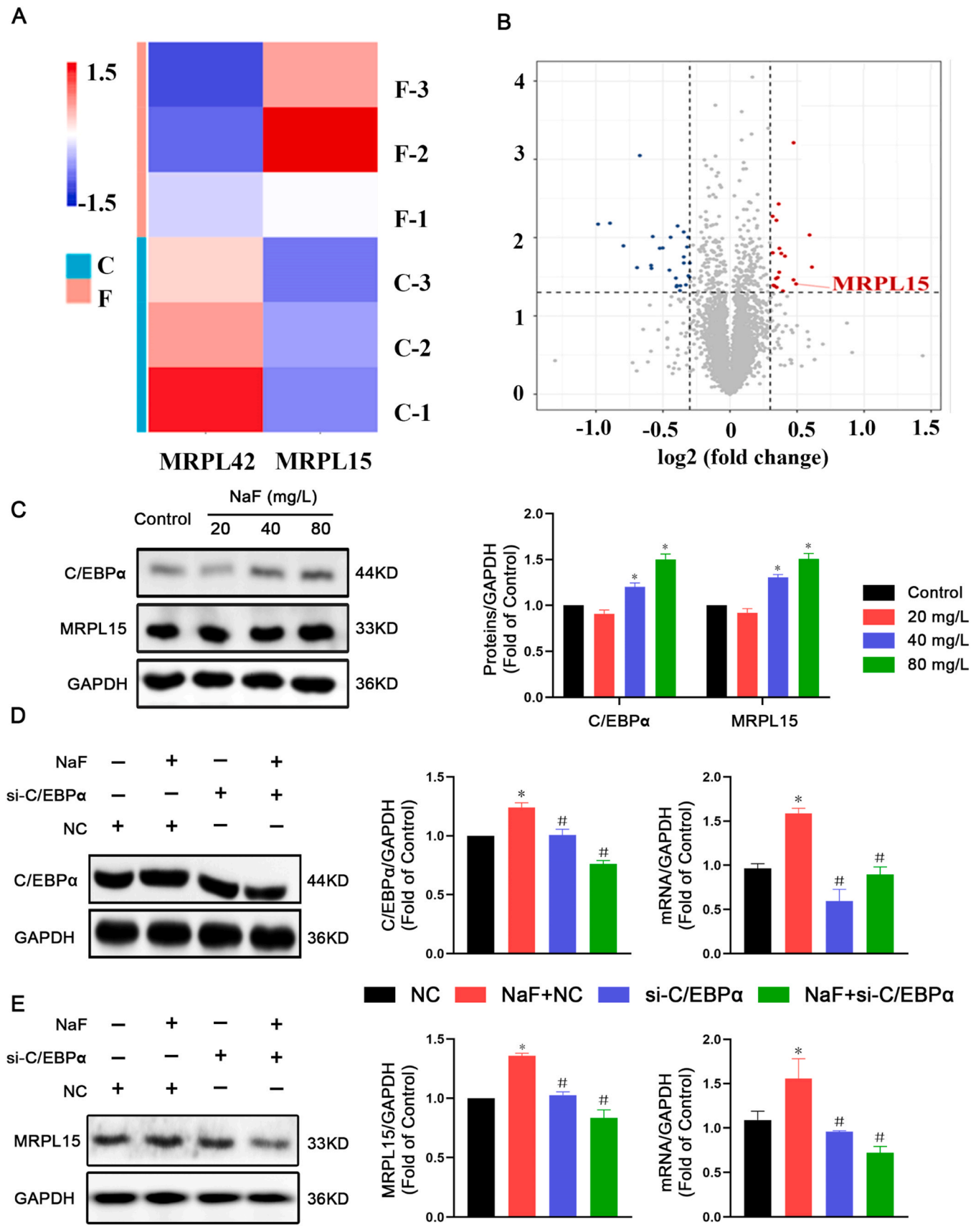

Fig. 2. Fluoride affected the levels of MRPL15 expression through C/EBPα in PC12 cells. (A) Differentially expressed proteins in the mitochondrial ribosomes of the hippocampal tissue of SD rats. (B) Volcano plot of differential protein expression. (C) Western blot analysis of MRPL15 and C/EBPα in PC12 cells, with GAPDH as a control. (D) Western blot and RT-qPCR analysis of C/EBPα in PC12 cells, with GAPDH used as a control. (E) Western blot and RT-qPCR analysis of MRPL15 in PC12 cells, with GAPDH used as a control. The data are presented as the means ± S.D.s of three replicates. Significance: $^{*}P < 0.05$ vs. NC, $\#P < 0.05$ vs. NaF + NC.

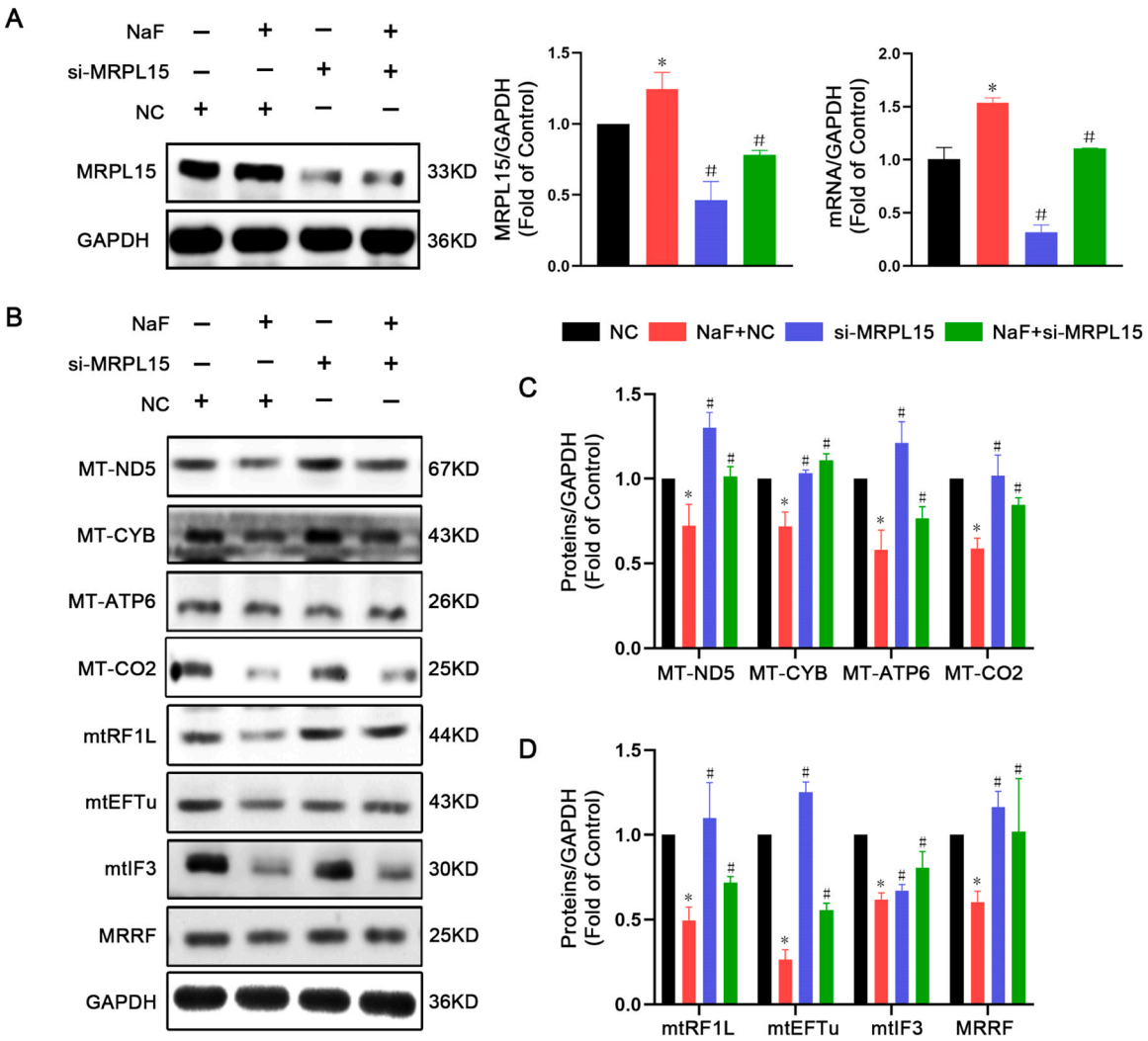

Fig. 3. MRPL15 knockdown partially alleviated the dysfunction of mitochondrial translation caused by fluoride in PC12 cells. PC12 cells were treated with siRNA and exposed to 80 mg/L NaF to knockdown MRPL15. (A) Western blot and RT-qPCR analysis of MRPL15 in PC12 cells, with GAPDH used as a control. (B) Western blot of mitochondrial translation factors and mitochondrial translation products in MRPL15-knowdown PC12 cells. (C) Analysis of mitochondrial translation factors, with GAPDH used as a control. (D) Analysis of mitochondrial translation products, with GAPDH used as a control. The data are presented as the means ± S.D.s of three replicates. Significance: $^{*}P < 0.05$ vs. NC, $\#P < 0.05$ vs. NaF + NC.

(Lightowlers et al., 2014; Xu et al., 2021).In neurodegenerative diseases, dysregulated MRPL15 expression is closely associated with mitochondrial translational defects: Aberrant MRPL15 expression in AD patient brains exacerbates Aβ-induced mitochondrial dysfunction (Gao et al., 2021). The aggregation of α-Synuclein suppresses MRPL15 expression, impairing respiratory chain integrity in dopaminergic neurons and contributing to PD pathogenesis (Bose and Beal, 2016). Genome-wide association studies (GWAS) further link the MRPL15 locus (chr8q24.3) to schizophrenia risk (Stahl et al., 2019), underscoring its broad involvement in central nervous system disorders. Notably, in environmental toxicology, the role of MRPL15 remains underexplored. Our study provides the first evidence that fluoride—a pervasive environmental neurotoxicant—upregulates MRPL15 to disrupt mitochondrial translation, subsequently triggering pyroptosis and cognitive impairment. This novel mechanism bridges mitochondrial proteostatic dysfunction with environmental toxin-induced neurotoxicity, offering critical insights for mitigating fluorosis-related health risks in endemic regions.

MtROS can induce mtDNA damage and promote its release into the cytoplasm, thereby activating the NLRP3 inflammasome (VanPortfliet et al., 2024),(Zhong et al., 2018). Reducing or obstructing the interaction between mtDNA and NLRP3 inflammasomes can influence the activation of subsequent pathways related to pyroptosis Under oxidative stress, mtROS disrupts the disulfide bond between thioredoxin-interacting protein (TXNIP) and thioredoxin-2 (TRX2) (Hwang et al., 2014; Tsubaki et al., 2020). leading to the binding of free TXNIP to the leucine-rich repeat (LRR) region of NLRP3, which drives inflammasome assembly and initiates pyroptosis (Tsubaki et al., 2020). Further studies reveal that ROS exacerbates NLRP3 production by activating the Pink1/Parkin pathway, ultimately resulting in cell death (Liu et al., 2024a). Research demonstrates that blocking the interaction between mtDNA and NLRP3 effectively suppresses subsequent pyroptosis pathways (Shimada et al., 2012). Consistent with these findings, our study shows that silencing C/EBPα and MRPL15 significantly alleviates fluoride-induced mtROS accumulation, thereby inhibiting NLRP3 generation and attenuating pyroptosis. This work establishes, for the first time, a molecular link between mitochondrial translational dysfunction (mediated by MRPL15) and pyroptosis activation, providing novel mechanistic insights into fluoride-induced neurotoxicity. MRPL15 may serve as an early warning biomarker for fluoride-associated neural injury. Targeting the C/EBPα-MRPL15 axis could offer a specific neuroprotective strategy for populations in high-fluoride areas. Moreover,

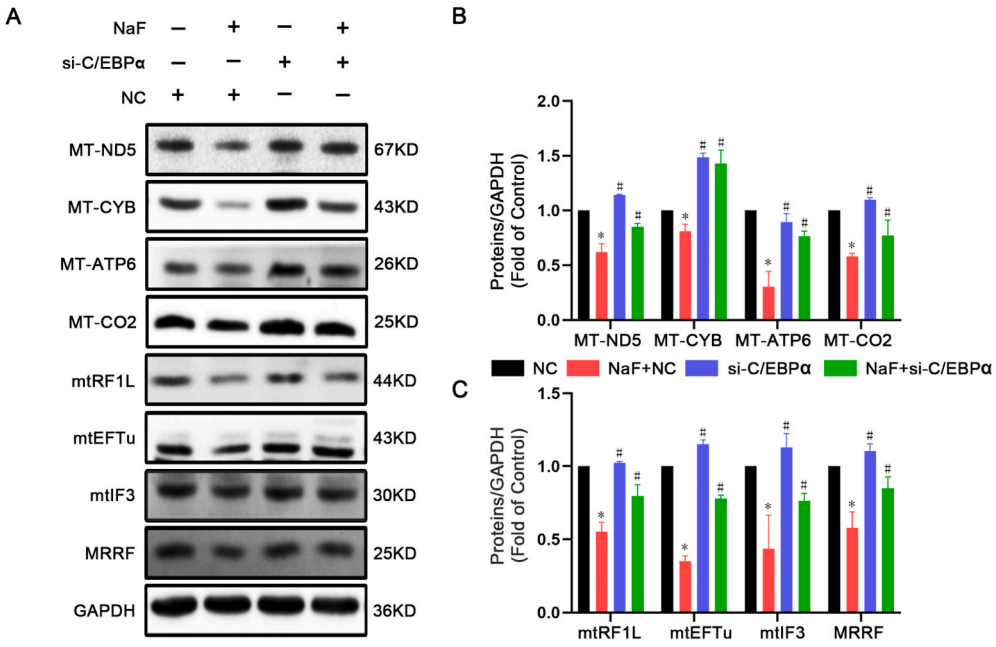

Fig. 4. C/EBPα knockdown partially alleviated the dysfunction of mitochondrial translation caused by fluoride in PC12 cells. PC12 cells were treated with siRNA and exposed to 80 mg/L NaF to knockdown C/EBPα. (A) Western blot of mitochondrial translation factor and mitochondrial translation product proteins in C/EBPα-knowdown PC12 cells. (B) Analysis of mitochondrial translation factors, with GAPDH used as a control. (C) Analysis of mitochondrial translation product proteins, with GAPDH used as a control. The data are presented as the means ± S.D.s of three replicates. Significance: $^{*}P < 0.05$ vs. NC, $\#P < 0.05$ vs. NaF + NC.

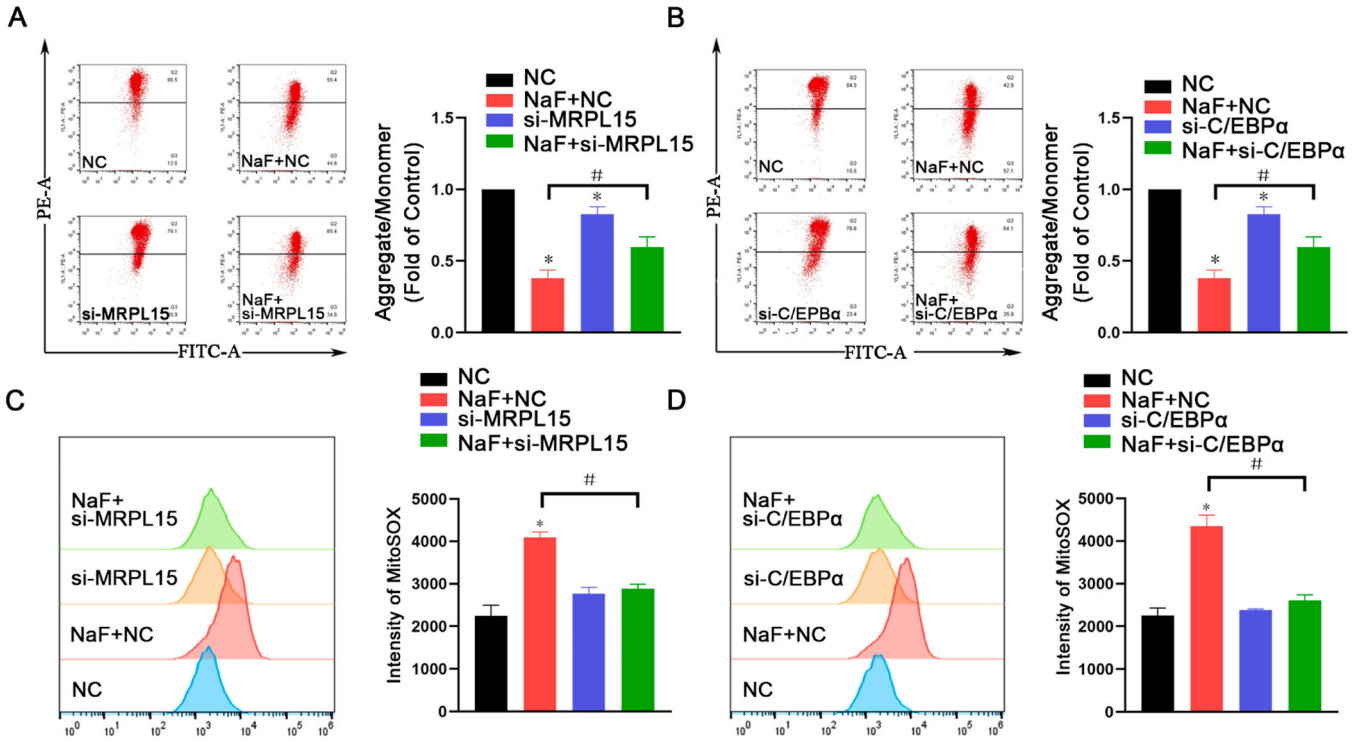

Fig. 5. Mitochondrial translation restoration attenuates fluoride-mediated neuronal injury. PC12 cells were treated with siRNA and exposed to 80 mg/L NaF to knockdown MRPL15 or C/EBPα. (A, B) Flow cytometry analysis of PC12 cells stained with JC-1. (C, D) Flow cytometry analysis of PC12 cells stained with MitoSOX Red. The data are presented as the means ± S.D.s of three replicates. Significance: $^{*}P < 0.05$ vs. NC, $\#P < 0.05$ vs. NaF + NC.

this axis—along with mitochondrial translational homeostasis—may serve as both an early risk indicator and a potential target for intervention. Future investigations should explore whether other environmental toxins (e.g., lead, polycyclic aromatic hydrocarbons) interfere with mitochondrial translation through similar mechanisms.

IL-1β, a product of pyroptosis, has been extensively studied as a therapeutic target for various systemic and localized inflammatory diseases, collectively known as autoinflammatory diseases. Increased release of mature IL-1β triggers a more extensive inflammatory reaction throughout the body, and studies have shown an association between

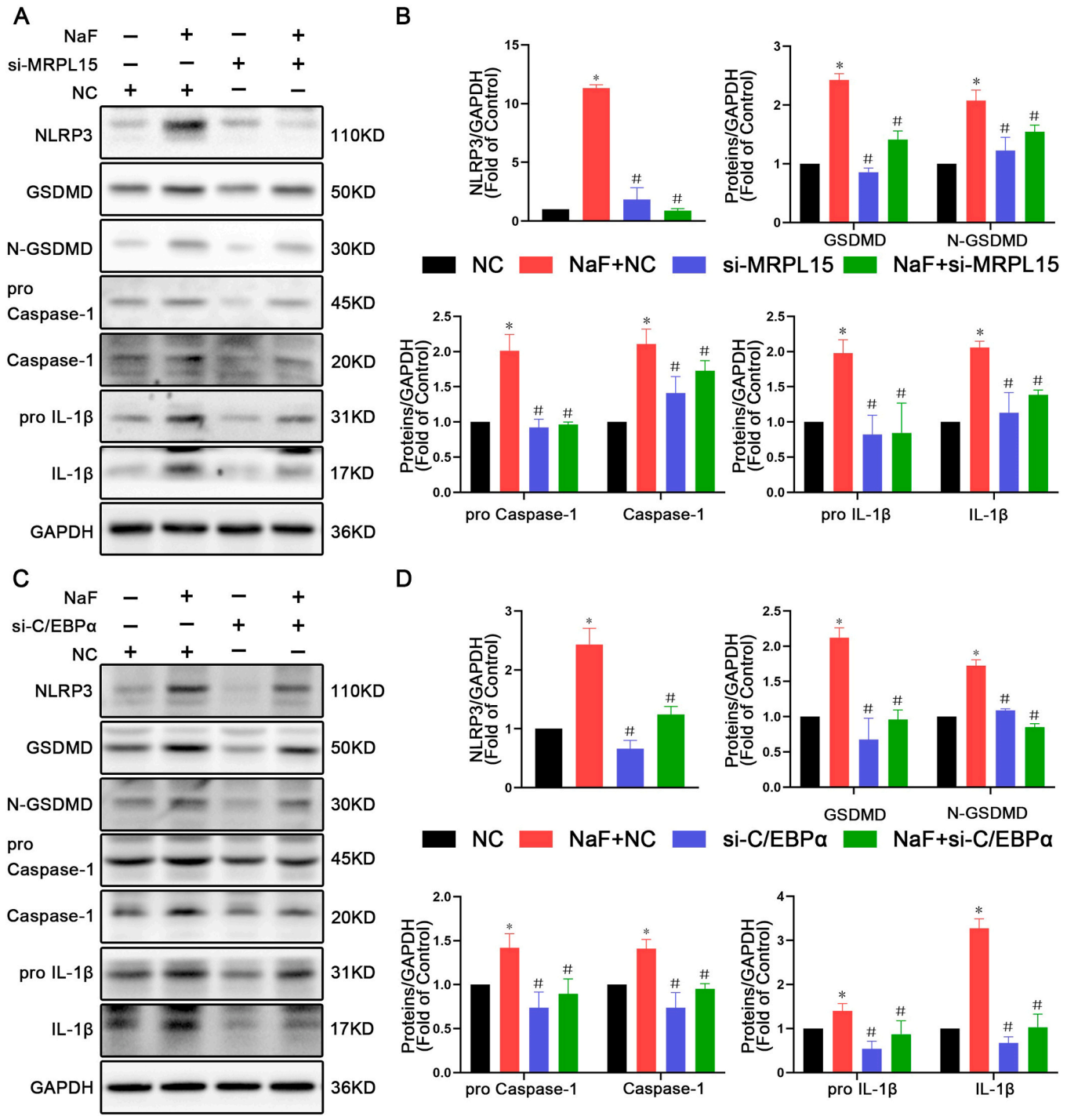

Fig. 6. Mitochondrial translation restoration attenuates fluoride-mediated pyroptosis. PC12 cells were treated with siRNA and exposed to 80 mg/L NaF to knock-down MRPL15 or C/EBPα. (A, C) Western blot of pyroptosis-related proteins, with GAPDH used as a control. (B, D) Analysis of pyroptosis-related proteins. The data are presented as the means ± S.D.s of three replicates. Significance: $^{*}P < 0.05$ vs. NC, $\#P < 0.05$ vs. NaF + NC.

elevated levels of IL-1β and stress-related neurological disorders (Dinarello, 2011; Qasim et al., 2024). Inflammation is an important part of neurotoxicity. Hippocampal inflammation is associated with post-operative cognitive decline in mature rodents, and slowing the occurrence and development of hippocampal neuroinflammation can effectively improve memory loss and cognitive impairment in test animals (Cibelli et al., 2010; Feng et al., 2017; Wan et al., 2007). The maternal inflammatory response can affect fetal nervous system development until childhood, resulting in neurodevelopmental delay (Han et al., 2021; John et al., 2017; Stewart and Beart, 2016). These findings are consistent with the results of our previous population survey, which revealed that exposure to low concentrations of fluoride can lead to an increase in serum inflammatory factor levels in school-aged children (Tang et al., 2023a). Thus, in this study, we established a fluoride-exposed rat model and observed that the severity of cognitive deficits was positively correlated with the hippocampal levels of pyroptosis-related proteins. Integrating these findings with our mechanistic data, it is plausible that neuroinflammation driven by the C/EBPα-MRPL15-mtROS axis via pyroptotic signaling may contribute to fluoride-induced cognitive impairment. Blocking the inflammatory

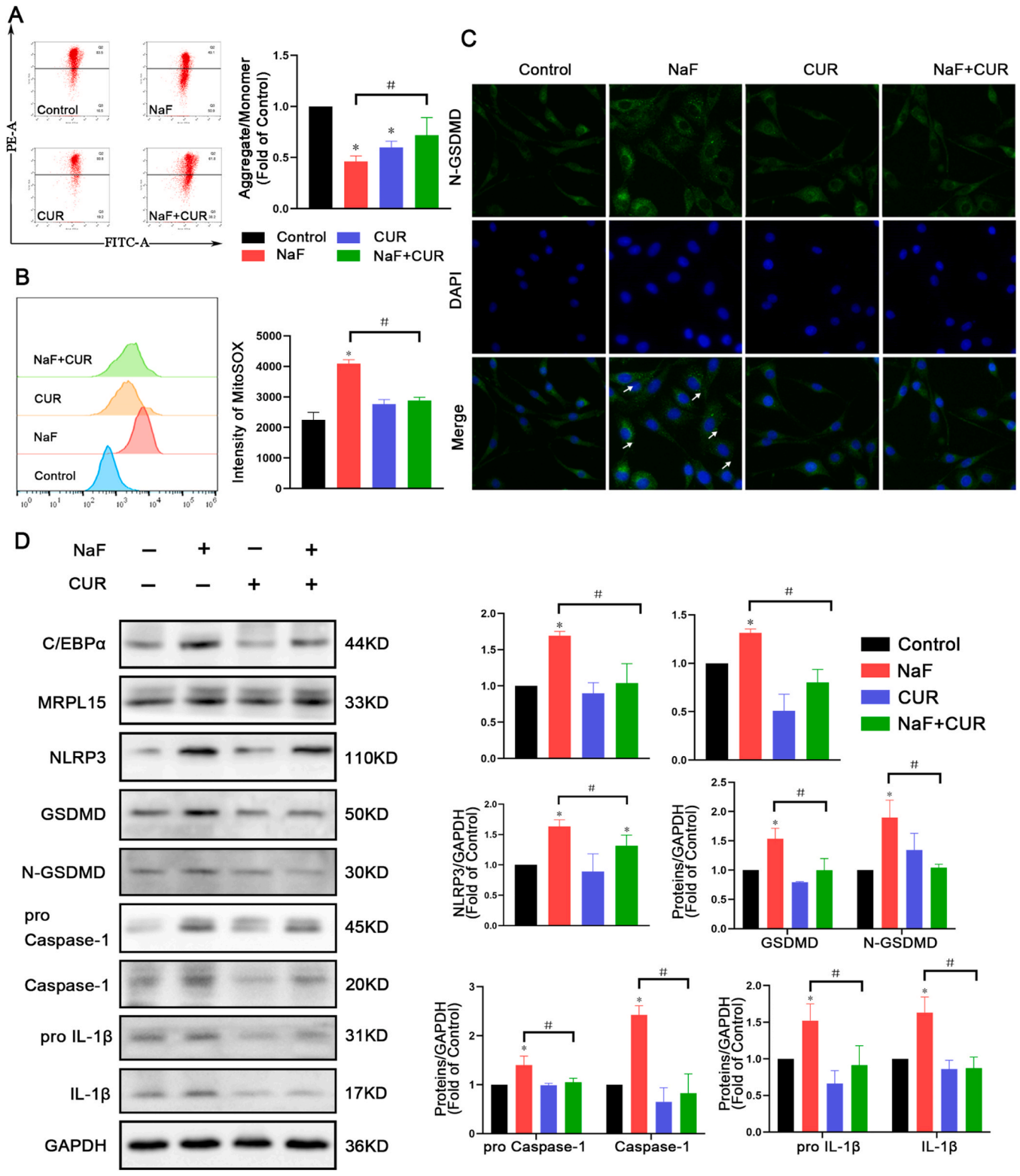

Fig. 7. CUR rescued PC12 cells from damage caused by fluoride. PC12 cells were subjected to 24 h of treatment with 10 μmol/L CUR, followed by 24 h of exposure to 80 mg/L NaF. (A) Analysis of PC12 cells stained with JC-1 was conducted via flow cytometry. (B) Flow cytometry was utilized to analyze PC12 cells stained with MitoSOX Red. (C) Representative images showing N-GSDMD localization (green) in PC12 cells stained with DAPI (blue), 40X. White arrows: cells with ruptured membranes. (D) Western blot and analysis of pyroptosis-related proteins. The data are presented as the means ± S.D.s of triplicate samples; $*P < 0.05$ vs. the control. $\#P < 0.05$ vs. NaF + CUR.

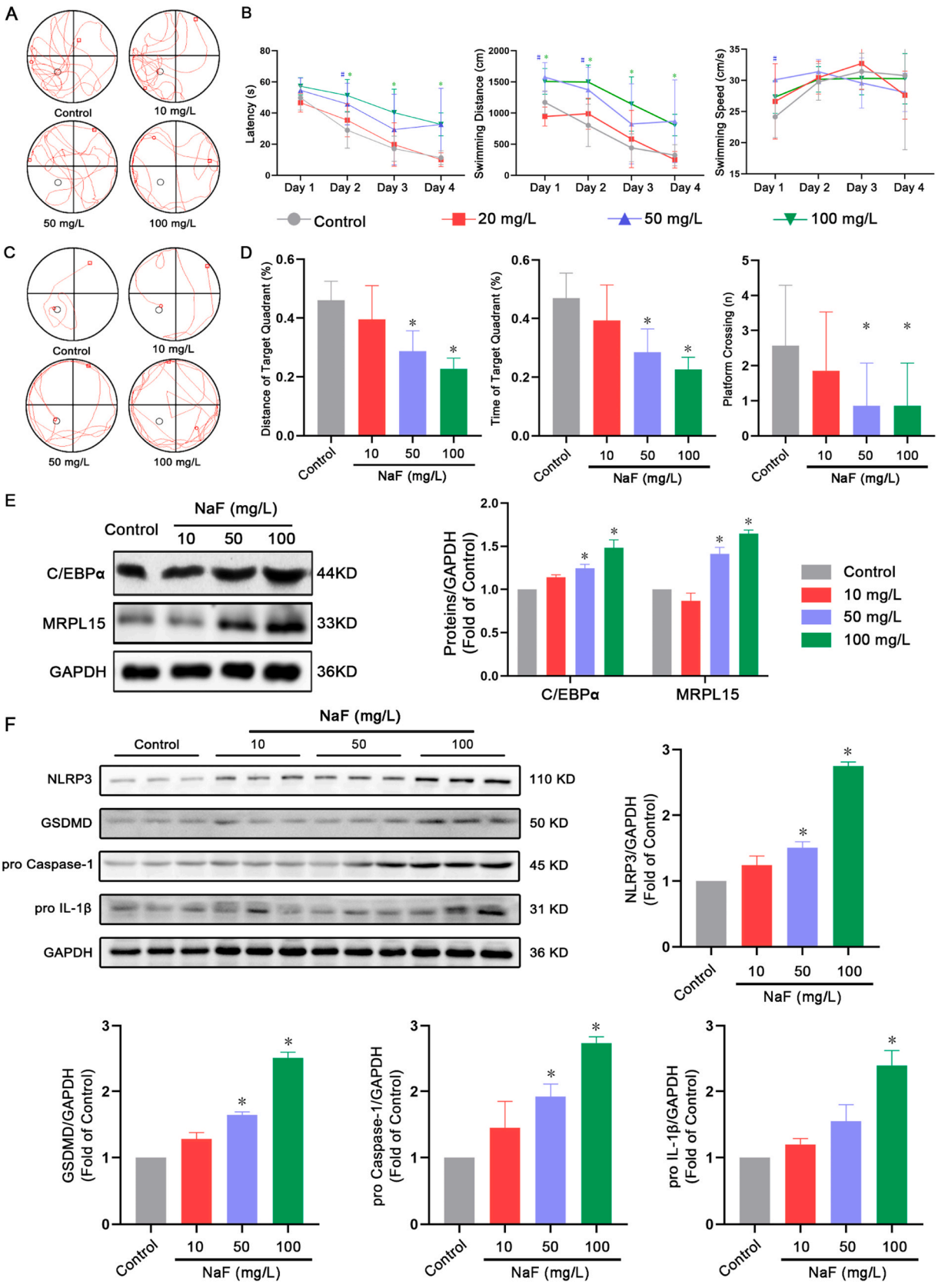

Fig. 8. Fluoride led to impaired cognitive ability and pyroptosis in offspring of SD rats. (A) Latency to reach the platform. (B) Swimming distance and swimming speed toward the platform were measured, and representative paths of the SD rats were measured on the fourth day of the navigation test. (C) Paths of SD rats during the spatial probe test. (D) Distance and time spent in the quadrant with the hidden platform during the spatial probe test were recorded, and the frequency of crossing the target quadrant during the spatial probe test was noted. (E) Western blot analysis of MRPL15 and C/EBPα in SD rats. (F) Western blot analysis of pyroptosis-related protein expression levels, with GAPDH used as a control. The data are presented as the means ± S.D.s of 5 replicates; *$P < 0.05$ vs. the control.

cascade may represent a novel therapeutic direction for mitigating fluorine-induced neurotoxicity.

To our knowledge, this study represents the first report elucidating the mechanistic role of neuroinflammation in fluoride-induced cognitive impairment. Neuroinflammation has been demonstrated to play a pivotal role in cognitive decline and functional deficits associated with neuronal damage (Heneka et al., 2015; Hou et al., 2021). Hippocampal inflammation has been linked to postoperative cognitive dysfunction in adult rodents, while attenuating neuroinflammatory progression effectively improves memory loss and cognitive deficits (Cibelli et al., 2010; Feng et al., 2017; Wan et al., 2007). Notably, fluoride exposure has been shown to induce neuroinflammation and subsequent neuronal injury (Chen et al., 2017; Yıldız et al., 2022). Consistent with these findings, our previous population-based survey identified elevated serum inflammatory cytokine levels in fluorosis-affected school-aged children with intellectual deficits (Tang et al., 2023b), strongly implicating neuroinflammatory cascades in fluoride-induced neural damage. Critically, integrating our mechanistic insights with epidemiological evidence could validate the "fluoride-inflammation-cognitive impairment" translational axis, thereby informing novel therapeutic strategies for fluorosis mitigation. Furthermore, the selection of doses for both *in vivo* and *in vitro* experiments in this study was thoroughly justified. The *in vivo* dosage was determined based on preliminary studies and converted from epidemiological research data, which allows for an accelerated simulation of the effects of lifetime cumulative exposure in high-risk populations(Reagan-Shaw et al., 2008). The doses used in the *in vitro* studies were not merely equivalent conversions of the *in vivo* doses but were instead empirically determined based on *in vivo* results, prior research, and the practical implications of dose setting, validated through CCK-8 assays(Barbier et al., 2010; Whitford, 1996). The *in vitro* results demonstrated consistent dose-response effects across various endpoints (mitochondrial translation, mtROS, pyroptosis), supporting the biological relevance of the selected concentration range and providing important reference values for future preclinical translational research.

CUR, a natural anti-inflammatory compound, is extensively utilized in clinical therapy. In this study, CUR diminished the upregulation of pyroptosis-related proteins induced by fluoride through the C/EBPα-MRPL15-mtROS axis. CUR significantly mitigated the cell membrane rupture caused by pyroptosis. To improve the quality of life for populations residing in regions with high fluoride concentrations, it is imperative to identify and implement effective preventative measures against fluoride-related health risks.

Although our study has obtained consistent directional evidence from *in vivo* behavioral and *in vitro* genetic interventions, along with supportive pharmacological evidence of reversibility, several limitations should be acknowledged. First, while the causal relationship between fluoride-induced mitochondrial translational disruption and cognitive deficits is strongly supported by our data, it would be further strengthened by direct *in vivo* genetic evidence, such as hippocampus-specific knockdown of C/EBPα or MRPL15 in animal models. Moreover, this study lacks population data from endemic fluorosis areas, which limits the direct extrapolation of our findings to public health contexts. Future studies are warranted to correlate biomarkers of mitochondrial translation (e.g., MRPL15 expression in peripheral blood mononuclear cells) with cognitive performance in populations exposed to high fluoride levels.

Authors' contributiont

Wenhui Liu: Investigation, Methodology, Writing – original draft. **Chenxi Wang**: Investigation. Huayang TANG: Investigation, Data curation. Zhiyuan Tian: Methodology. Dongjie Li: Data curation. **Gaoshuai Chen:** Data curation**.** Aiguo Wang: Conceptualization, Validation, Writing – review & editing.

Each author has approved the submitted version (and any substantially modified version involving their contribution to the study) and agrees to the following:

(a) be personally accountable for their own contributions;

(b) ensure that questions regarding the accuracy or integrity of any part of the work—including those unrelated to their direct involvement—are appropriately investigated, resolved, and that the resolution is documented in the literature.

CRediT authorship contribution statement

Wenhui Liu: Writing – original draft, Methodology, Investigation. **Chenxi Wang:** Investigation. **Huayang Tang:** Investigation, Data curation. **Zhiyuan Tian:** Methodology. **Dongjie Li:** Data curation. **Gaoshuai Chen:** Data curation. **Aiguo Wang:** Writing – review & editing, Validation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.119187.

Data availability

The data that has been used is confidential.

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