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Corresponding author(s): Kelong Fan

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Tissue sections were imaged by the digital pathology slide scanner (Leica CS2, Germany). Confocal laser scanning microscopy images were obtained by fluorescence microscope (Olympus FV3000RS, Japan) or fluorescence microscope (Zeiss LSM980, Germany). Flow cytometry data were collected by FACS CaliburTM, Becton Dickinson (USA). Manganese concentrations were measured using Inductively Coupled Plasna Mass Spectrometry (ICP-MS) on the NexION 1000 system (USA). mRNA expression levels were detected using the QuantStudioTM 7 Flex system (Thermo Scientific, USA). Western blot results were captured using the enhanced chemiluminescence (ECL) system (Touch imager, E-blot, China). Electron microscopy images were obtained through transmission electron microscopy (Spirit, USA). Animal behavior data were collected by rotarod apparatus (SansBio, SA102, China) and square arena with an infrared detector (SansBio, SA215S, China). RNA-seq: raw data in fastq format were first processed to clean data by removing reads containing adapters via Cutadapt (v4.4). UV-vis absorption spectra were recorded using a Lambda 1050+ Ultraviolet spectrometer (PerkinElmer, USA). Fluorescence spectra were measured with an FL 8500 Fluorescence spectrometer (PerkinElmer, USA). X-ray photoelectron spectroscopy (XPS) spectra were acquired using a Thermo Escalab 250Xi (Thermo Fisher Scientific, USA). Proton magnetic resonance (1H NMR) spectra were recorded on an DD2 600 Hz spectrometer (Agilent, USA, with D2O as the solvent). XRD data and ESR spectra were collected by using a Bruker D8ADVANCE (Germany) with a scan rate of 6 ° / min and a Bruker A300-9.5/12 (Switzerland). FT-IR spectra were obtained using a Bruker INVENIO-S spectrometer (Bruker, Germany). Spherical aberration-corrected transmission electron microscope (AC-TEM) images were captured using a FEI Themis Z (Thermo Fisher Scientific, USA). All the calculations were performed using the Vienna Ab initio Simulation Package (VASP). The XAFS spectra were recorded with the specific detectors in the beamline 1W1B of Beijing Synchrotron Radiation Facility (BSRF), China. Transmission mode was adopted to collect the XAFS for the reference samples of Mn and the Mn@CDs. XAFS data were normalized and analyzed with least-squares fitting (LSF) to fit the spectra and to calculate the coordination structure for Mn using the IFEFFIT Athena software (CARS, the Consortium for Advanced Radiation Sources at University of Chicago, IL, USA).
Data analysis	General statistical data were analyzed by Athena, Artemis, Origin 2021, Nano Measurer 1.2, MestReNova 5.3.1-4696, XPSPEAK41,

DigitalMicrograph 3.7.4, VESTA, ImageJ (v1.52), FlowJo_V10, HISAT2 (v2.2.1) and Graphpad prism 8.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data supporting the findings of this study are available from the corresponding authors upon request. The RNA-seq data have been deposited in the NCBI Gene Expression Omnibus (GSE289958). Source data for the figures and supplementary figures are provided as a Source Data file. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes and repicates were determined based on previous studies and the requirements of each experiment, as detailed in the figure legends. The variation in sample size, particularly the number of mice used, was guided by the 3R principles (Replacement, Reduction, and Refinement) to uphold animal ethics.
Data exclusions	No data was excluded from the analysis.
Replication	Independent replicates of at least 3 times were used for all experiments. We confirmed that the attempts at replication were successful. Each figure contains detailed independent experimental replicates in the figure.
Randomization	All samples were randomly allocated into experimental groups.
Blinding	Blinding is not applicable for the synthesis and characterization of nanomaterials. For in vivo experiments, all the investigators were blinded to group allocation during data collection and analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
	x Antibodies
	x Eukaryotic cell lines
x	Palaeontology and archaeology
	x Animals and other organisms
x	Clinical data
x	Dual use research of concern
x	Plants

Methods

n/a	Involved in the study
x	ChIP-seq
	x Flow cytometry
x	MRI-based neuroimaging

Antibodies

Antibodies used

anti-GFAP antibody (Servicebio, GB11096)
anti-Iba1 antibody (Servicebio, GB12105)
HRP-conjugated goat anti-mouse secondary antibody (ZSBG-BIO, PV-6002)
HRP-conjugated goat anti-rabbit secondary antibody (ZSBG-BIO, PV-6001)
anti-ChAT antibody (Proteintech, 20747-1-AP)
anti-GFAP antibody (CST, 12389)
anti-Iba1 antibody (CST, 17198)
anti-Nrf2 antibody (CST, 12721)
anti-HO-1 antibody (Proteintech, 10701-1-AP)
anti-NQO1 antibody (Santa Cruz, sc-376023)
anti-GCLC antibody (Santa Cruz, sc-166356)
anti-GCLM antibody (Santa Cruz, sc-55586)
anti-synaptic vesicle protein 2 antibody (DSHB, SV2)
anti-neurofilament antibody (Sigma, SAB4200740)
anti-NDUFB8 antibody (Proteintech, 14794-1-AP)
anti-SDHB antibody (Proteintech, 10620-1-AP)
anti-actin antibody (ABclonal, AC004)
Alexa 488-labeled secondary antibody (Thermo Scientific, A11001)
HRP-conjugated goat anti-rabbit IgG (H+L) secondary antibody (Emarbio, EM35111)
HRP-conjugated goat anti-mouse IgG (H+L) secondary antibody (Emarbio, EM35110)

Validation

We reviewed the validation statements provided on the manufacturer's website for each antibody, confirming their specificity and suitability for our experimental conditions, We referenced studies in the literature that have utilized these antibodies in similar applications, providing evidence of their effectiveness and reliability in the desired contexts.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

SH-SY5Y cells were obtained from the American Type Culture Collection and were cultured in DMEM-F12 supplemented with 10% FBS supplemented with 1% penicillin–streptomycin.
NSC-34 cells were obtained from Hongshun Biotechnology Co., Ltd. (Shanghai, China) and were cultured in DMEM supplemented with 10% FBS supplemented with 1% penicillin–streptomycin.

Authentication

The cell lines were authenticated by STR profiling

Mycoplasma contamination

The cell lines were verified to be mycoplasma negative

Commonly misidentified lines
(See ICLAC register)

There are no commonly misidentified cell lines used in this study

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals

Male hemizygous SOD1G93A-Tg mice [B6. CgTg(SOD1*G93A)1Gur/J] (stock no. 004435) were purchased from the Jackson Laboratory (Maine, USA) and bred with female wild-type C57BL/6J mice to continue the species. Polymerase chain reaction (PCR) was conducted for genotyping neonatal mice according to the guidelines of the Jackson Laboratory (https://www.jax.org/strain/004435). The littermates with a nontransgenic genotype were regarded as wild-type healthy controls.

Wild animals

The study did not involve wild animals.

Reporting on sex

In behavioral experiments, each group was assigned 6 females and 4 males. In the verification of tissue sections, all mice were female

Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	The ethics oversight is subject to the approval and guidance of the Institutional Animal Care and Use Committee of the Institute of Biophysics, Chinese Academy of Sciences.(SYXK2023177)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

Flow Cytometry

Plots

Confirm that:

- [x] The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- [x] The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- [x] All plots are contour plots with outliers or pseudocolor plots.
- [x] A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For cellular ROS generation assay, the cells were seeded in 12-well plates overnight (30,000 cells per well for NSC-34 cells and 20,000 cells per well for SH-SY5Y cells). The cells were preincubated with Mn@CDs (20 μg/mL) for 2 h and subsequently stained with DHE, DCFH-DA , or MitoSOX Green following the manufacturer's protocols. After that, the cells were stimulated with PQ for 24 h or stimulated with H2O2 for 4 h. After treatment, the cells were washed with PBS, collected, and analyzed with a FACS Calibur For cell apoptosis analysis, The cells (30,000 cells per well for the NSC-34 cells and 20,000 cells per well for the SH-SY5Y cells) were seeded in 12-well plates overnight. After preincubation with Mn@CDs (20 μg/mL) for 2 h, the cells were treated with H2O2 for 12 h (for NSC-34 cells) or 8 h (for SH-SY5Y cells). The cells were subsequently collected and resuspended in Annexin V binding solution and stained with Annexin V-FITC and propidium iodide (PI) for 15 min at room temperature. After staining, the cells were washed and resuspended in Annexin V binding solution until detection via a FACSCalibur. For cellular Ca2+ concentration detection, The cells (30,000 cells per well for NSC-34 cells and 20,000 cells per well for SH-SY5Y cells) were seeded in 12-well plates overnight, followed by pretreatment with Mn@CDs (20 μg/mL) for 2 h. Subsequently, the cells were incubated with H2O2 for 4 h. Fluo-4 AM was utilized for staining, and a FACS Calibur was used for detection.
Instrument	FACS CaliburTM, Becton Dickinson, Franklin Lakes, NJ,USA
Software	FlowJo 10
Cell population abundance	We collected at least 10000 cells per samples for test.
Gating strategy	Cells were gated based on size and granularity of forward and side scatter (SSC and FSC) and the cell gate is analyzed for specific fluorescence.

- [x] Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.