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Reporting Summary

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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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

Western blotting was performed using a ChemiDoc MP imaging system (Bio-Rad, 12003154 Hercules, CA, USA). The morphology of lipid nanoparticles was observed using a transmission electron microscope (H-7000FA, Hitachi LTD, Japan). The size and concentration of lipid nanoparticles were analyzed using a NANOSIGHT NS300 system (Malvern, UK). The stability of lipid nanoparticles was detected using Zeta potential analysis (Malvern Zetasizer Nano ZS90, UK). Flow cytometry analysis was performed using a FACSCalibur flow cytometer (BD Biosciences, USA). Mass spectrometry detection was performed using an Orbitrap Fusion Lumos (Thermo Scientific, USA).

Data analysis

Image j (V1.52v); Graph pad Prism 9.3.0; Stats R package (3.6.1); DESeq2 R package; Gene set enrichment analysis (GSEA) v4.2.3; Proteome Discoverer (V1.4)

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 RNA-seq, RIP-seq and ATAC-seq data generated in this study are available on the National Center for Biotechnology Information (NCBI) database under the BioProject number PRJNA1245287, PRJNA1245112 and PRJNA1245087. The proteomic datasets are available in Source Data files. Source data is available for Figs. 1b-d, f-g, n-o, 2b-e, h, j-q, 3c-d, j-l, o, 4g, 5a-c, 6g-h, j, 7f, k-l, 8c, g, l-m and Extended Data Figs. 1e-l, n, 2a-f, l 3i-l, 5b, e-i, 6g, i, 7b, d in the associated source data file. The information of the volunteers enrolled in the study, primer sequences used in PCR genotyping, siRNA sequences used in siRNA transfection and antibodies used in this study are provided in the Supplementary Information (Supplementary Tables 1, 2 and 3). All data supporting the findings of this study are available within the article and its supplementary files. Any additional requests for information can be directed to, and will be fulfilled by, the corresponding authors. 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

Our study design did not take sex and gender characteristics into account, but there were no differences in sex and gender characteristics among the human participants involved in our study.

Reporting on race, ethnicity, or other socially relevant groupings

Race, ethnicity or other socially relevant groupings were not considered in our study design.

Population characteristics

NP tissue samples were obtained from patients with scoliosis, lumbar disc herniation or lumbar spinal stenosis who underwent orthopedic surgery involving lumbar segments. There were 12 male patients and 12 female patients, with age ranging from 12 to 61 years.

Recruitment

Healthy NP tissue samples were obtained from patients with scoliosis who underwent orthopedic surgery involving the lumbar segment, and the IVD tissue was rated as grade I by the Pfirrmann grading system of MRI-T2 weighted images. Degenerated NP tissue samples were obtained from patients with lumbar disc herniation who underwent discectomy, and the IVD tissue was rated as grade III to IV by the Pfirrmann grading system. In addition, some patients who did not have cardiovascular and cerebrovascular diseases, cancer, infection, immune and endocrine diseases or organ dysfunction agreed to use NP tissue samples for scientific research. Three pairs, including three non-denatured and denatured samples, were used for transcriptome RNA sequencing. However, the inevitable operational errors during sampling may cause the results to be inconsistent with the actual degree of illness of the patient, thereby affecting the research results and deviating slightly from the actual situation.

Ethics oversight

All ethical aspects related to the experimental design and implementation in this study, including the consultation of patient medical records, collection and use of NP tissue samples, surgical procedures, and sample collection, were approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Approval No. S341).

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](https://www.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

No statistical method was used to predetermine the sample size. The sample size was determined based on previous studies of similar experiments (Nature Communications vol. 9, 15051. November 28, 2018; Nature Communications vol. 12, 15213. September 3, 2021; Nature Communications 13, 11469. March 18, 2022). All experiments were performed at least 3 separate technical experiments or at least 3 biological samples were replicated, which allowed sufficient statistics for unpaired t-tests or ANOVA analyses, and the p values indicated significance.

Data exclusions

No data was excluded.

Replication

All the experiments were replicated. In general, at least three separate technical experiments or at least triplicate biological samples were performed determined based on the experiments.

Randomization

All samples were randomly assigned, and analyzed together in each experiment

Blinding

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

The information of all the antibodies used in the study were listed in the Supplementary Table 2.

Validation

The validation information of all the antibodies could be searched in the manufacturer's websites according to the source and identifier:

anti-Aggregan, Affinity, DF7561, WB (1: 500), https://www.affbiotech.cn/goods-11320-DF7561-Aggregan_Antibody.html

anti-Collagen II, Affinity, AF5456, IHC (1:100), IF (1:100), WB (1:500), https://www.affbiotech.cn/goods-4762-AF5456-Collagen_II_Antibody.html

anti-MMP3, Affinity, AF0217, IHC (1:100), IF (1:100), WB (1:500), https://www.affbiotech.cn/goods-88-AF0217-MMP3_Antibody.html

anti-Adams5, Affinity, DF13268, WB (1: 500), https://www.affbiotech.cn/goods-16646-DF13268-ADAMTS5_Antibody.html

anti-DDX1, Proteintech, 11357-1-AP, WB (1: 1000), IF (1:300), IP (4µg/1000µg), <https://ptgcn.com/results?category=&q=11357-1-AP&target=>

anti-Mono Methyl Lysine, CST, 14679, WB (1: 1000), <https://www.cellsignal.cn/products/teomonic-analysis-products/mono-methyl-lysine-mme-k-multimab-rabbit-mab-mix/14679>

anti-EZH2, Abcam, ab307646, IHC (1:200), IF (1:400), WB (1: 500), IP (4µg/1000µg), <https://www.abcam.cn/products/primary-antibodies/kmt6--ezh2-antibody-epr25353-284-ab307646.html>

anti-GAPDH, Proteintech, 60004-1-Ig, WB (1: 2000), <https://ptgcn.com/results?category=&q=60004-1-Ig&target=>

anti-β-actin, Proteintech, 66009-1-Ig, WB (1: 2000), <https://ptgcn.com/results?category=&q=66009-1-Ig&target=>

anti-Bax Affinity, AF0120, WB (1: 500), https://www.affbiotech.cn/goods-45-AF0120-Bax_Antibody.html

anti-Caspase3, CST, 9661, WB (1: 500), <https://www.cellsignal.cn/products/primary-antibodies/cleaved-caspase-3-asp175-antibody/9661>

anti-Bcl-2, CST, 3498, WB (1: 500), <https://www.cellsignal.cn/products/primary-antibodies/bcl-2-d17c4-rabbit-mab/3498>

anti-p21, CST, 2947, IHC (1:150), IF (1:300), WB (1:500), <https://www.cellsignal.cn/products/primary-antibodies/p21-waf1-cip1-12d1-rabbit-mab/2947>

anti-P53, CST, 2527, WB (1: 500), <https://www.cellsignal.cn/products/primary-antibodies/p53-7f5-rabbit-mab/2527>

anti-P16, CST, 80772, WB (1:500), <https://www.cellsignal.cn/products/primary-antibodies/p16-ink4a-d7c1m-rabbit-mab/80772>

anti-Flag tag, Proteintech, 66008-4-Ig, WB (1: 1000), IP (4µg/1000µg), <https://ptgcn.com/results?category=&q=66008-4-Ig&target=>

anti-His tag, Proteintech, 66005-1-Ig, WB (1: 1000), IP (4µg/1000µg), <https://ptgcn.com/results?category=&q=66005-1-Ig&target=>

anti-GST tag, Proteintech, 66001-2-Ig, WB (1: 1000), IP (4µg/1000µg), <https://ptgcn.com/results?category=&q=66001-2-Ig&target=>

anti-HA tag, Proteintech, 66006-2-Ig, WB (1: 1000), IP (4µg/1000 µg), <https://ptgcn.com/results?category=&q=66006-2-Ig&target=>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Human embryonic kidney 293T cell line was purchased from the American Type Tissue Culture Collection.

Authentication

We performed cell line identification by STR genotype.

Mycoplasma contamination

This cell line was tested for mycoplasma contamination and was negative. The cell line was cultured in our laboratory and passaged more than 30 times after resuscitation. The contamination of Mycoplasma was routinely detected by PCR.

Commonly misidentified lines
(See [ICLAC](#) register)

There is no commonly misidentified cell lines in the 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	Two-month-old female SD rats weighing 200 ± 20 g were housed at the Experimental Animal Center of Huazhong University of Science and Technology under a 12:12 h light-dark cycle at 21°C.
Wild animals	The study didn't involve wild animals.
Reporting on sex	Only female rats participated in this experimental study.
Field-collected samples	The study didn't involve samples collected from the field.
Ethics oversight	Animal obtainment, animal surgical operation and animal sample collection, were approved by Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (No. S2394).

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

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.

Flow Cytometry

Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ 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).
- ☒ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cells were digested with EDTA-free trypsin (Macgene, CC035) for 3 minutes, then collected by centrifugation, washed with ice-cold phosphate-buffered saline (PBS), and resuspended in 100 μ l of 1 $\times$ binding buffer at a density of 5×10^5 cells/ml.
Instrument	CytoFLEX S (Beckman Coulter Life Science).
Software	CytExpert (version 2.4).
Cell population abundance	The abundance of target cell population in DSC and SSC channels reached more than 90%, and the rest were cell fragments.
Gating strategy	1) Cells in the normal group were set as the blank group, which were delineated by FITC-A and PI-A channels, respectively. 2). The fluorescence intensity of normal group was used as negative control group. 3). When FITC or PI was detected, the cell fluorescence intensity greater than 3000 was defined as the positive peak.

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