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Reporting Summary

Nature Research 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 Research 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	Nikon image-acquisition software: NIS Elements AR 4.60.00 (version 4.60); FEI Quanta 650 ESEM: XT Microscope Server; Gatan Microscopy Suite® (GMS);Leica SP8 confocal: Leica Application Suite X (LAS X); WB detection: ImageQuant TL 8.1; PCR analysis : BioRad CFX Manager 3.1.
Data analysis	MATLAB R2019a;Image J/FIJI (64-bit Java 1.8.0); OriginPro 8; Microsoft Excel(2016); GitHub Link for custom codes: https://github.com/BME2021/LineageSpecificResponsiveness/blob/main/LineageSpecificResponsiveness.ipynb

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The main data supporting the results in this study are available within the paper and its Supplementary Information. The raw and analyzed datasets generated during the study are too large to be publicly shared, yet they are available from the corresponding authors upon reasonable request.

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	No statistical method was used to predetermine sample sizes. Sample sizes were chosen to establish statistical significance on the basis of similar experiments reported in the literature (Liu et al., 10.1016/j.biomaterials.2016.09.023; Ihalainen et al., 10.1038/nmat4389; Downing at al., 10.1038/nmat3777). For the imaging studies, the number of cells analysed was estimated to achieve a 95% confidence level given the expected difference between the groups being tested.
Data exclusions	For qualified RNA-sequencing and RT-qPCR data, we excluded extracted RNA samples showing low quality and yield. TEM images that showed major sectioning artifacts were excluded.
Replication	All experimental findings were carried out in duplicate at least.
Randomization	Not applicable, because all cells were allocated into different groups according to the substrate topography.
Blinding	Blinding was not possible for most of the data acquisition and analysis. This is because the cell and the nuclear morphology of the groups being tested was evidently different and the image analysis required drawing ROI around the nuclei of the cells. Exception: Differential Gene Expression analysis of Bulk RNA-Seq was blinded.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	The detail information is provided in Supplementary Table S6 and S7.
Validation	All the antibodies used in this study were commercial antibodies and were only used for applications, with validation procedures described on the following sites of the manufacturers: https://www.thermofisher.com; https://www.abcam.com; https://www.cellsignal.com/, https://www.sigmaaldrich.com/, https://www.scbt.com/home,

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Human mesenchymal stem cells (hMSCs) were purchased from the American Type Culture Collection (ATCC), PCS-500-012, LOT: 70008843
Authentication	Authentication of hMSCs was performed by ATCC.
Mycoplasma contamination	A mycoplasma Removal Agent (Bio-rad, BUF035) was used to prevent mycoplasma contamination. The Hoechst/DAPI staining showed that all cells were free of mycoplasma contamination.

Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.