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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	Human GRCh38 and mouse mm10 genomes were used to map scRNA-seq and RNA-seq bulk reads to their corresponding genes
Data analysis	standard CellRanger pipeline (versions varied depending on the run from 3.0.0 to 3.0.1, 3.1.0 and more recently 6.0.0) to map reads onto the reference genome and get the gene expression count matrices per cell R (version 4.0.4) for all downstream analysis of the scRNA-seq data Seurat package (version 4.0.1) for basic QC and analysis of scRNA-seq data DoubletFinder (version 2.0.3), scDblFinder (version 1.4.0) and scds (hybrid mode, version 1.6.0) with default parameters to predict doublets in scRNA-seq data SoupX package (version 1.5.2) to correct for background noise in scRNA-seq data Harmony (version 0.1.0) to integrate all patient scRNA-seq samples together inferCNV package (version 1.11.2) to infer the copy number variation from the scRNA-seq data

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 scRNA-seq and bulk RNA-seq raw data generated in this study have been deposited at the Gene Expression Omnibus (GEO) under the accession code GSE221494 [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE221494]. The shallow WGS and targeted DNAseq raw data generated in this study have been deposited at the BioProject database under the accession code PRJNA113972 [http://www.ncbi.nlm.nih.gov/bioproject/1139721]. 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	Reporting on sex is provided in Supplementary Table 1 for each individual patient. Age and gender were not considered in the study design and gender of participants was determined based on self report.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable
Population characteristics	Population characteristics including age, sex, tumor location , tumor size, tumor grade and follow-up are provided in Supp Table 1
Recruitment	All patients naive of pre-operative treatment and undergoing surgery for primary DDLPS from 2019 to 2023 in our instution were included. All patients gave written informed consent.
Ethics oversight	Institut Curie institutional review board and ethics commitee approved the study protocol. All patients gave written informed consent. The study complies with all relevant ethical regulations and was approved by Institut Curie institutional review bord (IRB protocol DATA190160).

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	No sample-size calculation was performed. We decided to perfom scRNAseq on 10 WD and 10 DD components from DDLPS tumors, so as to have a comparable number of single cells from each component and a sufficient number of total cells to identify potential rare subpopulations.
Data exclusions	Concerning scRNAseq data, cells that did not complied to standard quality controls were filtered as standard procedure for scRNAseq analysis. No other data exclusion was performed.
Replication	Experimental findings were replicated in a least three independent experiments and the results of all replicates were consistent.
Randomization	not applicable: this study is not a clinical trial and describes the multiomic characterization of a cohort of human tumors
Blinding	not applicable: this study is not a clinical trial and describes the multiomic characterization of a cohort of human tumors

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

All antibodies are described in the method section:
For immunohistochemistry, Serial 5 µm sections were incubated with specific antibodies recognizing tumoral cells (MDM2, SantaCruz, ref sc965, pH6, dil 1:100), macrophages (CD163, Novocastra, ref NCL-L-CD163, clone 10D6, pH6, dil 1:100), lymphocytes (CD3, Dako Agilent, ref A0452, pH9, dil 1:100, FOXP3, Master Diagnostica, ref MAD-000536-QD, clone SP97, pH9, ready-to-use), and DDLPS progenitors (CD55, CST, ref 31759, clone E7G2U, dil 1 :600, pH 9).
For multiplex immunofluorescence; the following antibodies were used: lymphoid panel : CD4 (Cell signaling, ref 48274, dil 1: 100), FOXP3 (Diagomics, ref MAD-000536QD, ready-to-use (RTU)), CD8 (Agilent, ref M710301, dil 1: 200), PD1 (Abcam, ref ab137132, dil 1: 500), MDM2 (Diagomics, ref MAD-000682QD, RTU) ; myeloid panel : CD68 (Agilent, ref M081401, dil 1: 800), CD163 (Leica, ref NCLCD163, dil 1: 200), S100A8 (Abcam, ref ab92331, dil 1: 100), CD33 (Abcam, ref ab270942, ref 1: 500), MDM2 (Diagomics, ref MAD-000682QD, RTU) ; progenitor panel : CD55 (Cell signaling, ref 31759, dil 1: 800), CD44 (Abcam, ref ab189524, dil 1: 3,000), ALDH1 (BD Biosciences, ref 611194, dil 1: 1000), CD34 (Agilent, ref M716529, dil 1: 200), MDM2 (Diagomics, ref MAD-000682QD, RTU) ; TGF panel : TGF-β1 (Abcam, ref ab215715, dil 1: 100), CD3 (Agilent, ref ir503, RTU), CD14 (Abcam, ref ab182032, dil 1: 200), MDM2 (Diagomics, ref MAD-000682QD, RTU).
For Western Blott, the following antibodies were used: anti-Smad2 (CST, ref CS3122, dil 1 : 1,000), anti-Phospho-Smad2 (CST, ref CST3108, dil 1 : 1,000), anti-FABP4 (Abcam, ref ab92501, dil 1 :1000), anti-GAPDH (Proteintech, ref HRP-60004, dil 1 : 10,000)

Validation

MDM2 antibody: validated for detection of rat, mouose, and human MDM2 by WB, IF, IHC (Latif et al, Nat Com 2021)
CD163 antibody: validated for detection of human CD163 by IHC (Lau et al, American Journal of Clinical Pathology 2004)
CD3 antibody: validated for detection of human CD3 by IHC (Moritsch et al, Oncoimmunology 2022)
FOXP3 antibody: validated for detection of human FOXP3 by IHC (Suzuki et al, JCO 2012)
CD55 antibody: validated for detection of human CD55 by WB and IHC (Blood, Brodsky, Blood,2014)
For antibodies used for multiplex immunofluorescence, validation was performed within this study (see Methods section).
Smad2 antibody: validated for detection of human Smad2 by WB, IF and IP (Qiuhua Yang, et. al. Cells, 2023)
2023
Phospho-Smad2 antibody: validated for detection of human phospho Smad2 by WB (Kyungsoo Kim, et. al. Biotechnol J 2024)
FABP4 antibody: validated for detection of human FABP4 by WB, IHC and IF (Link et al, JCI 2022)
GAPDH antibody : validated for detection of human GAPDH by WB, IHC, IF (Yang, Nature 2020)

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

described in the method section:
PDX SIL10AS was established in Institut Curie and PDX 15lp0542, 15lp2584 and 15lp4728 were established in Institut Régional du Cancer de Montpellier . Models were obtained from consented DDLPS patients after IRB approval. Tumors were engrafted in nude mice, monitored weekly and collected before they reached 10,000 mm3. Mice were euthanized by cervical dislocation. Mice were purchased from Charles River Laboratories and maintained under specific pathogen-free conditions.

Wild animals

not applicable

Reporting on sex

All experiments were realized on 7 to 8 week-old female nude mice

Field-collected samples

described in the method section:
PDX SIL10AS was established in Institut Curie and PDX 15lp0542, 15lp2584 and 15lp4728 were established in Institut Régional du Cancer de Montpellier . Models were obtained from consented DDLPS patients after IRB approval. Tumors were engrafted in nude mice, monitored weekly and collected before they reached 10,000 mm3. Mice were euthanized by cervical dislocation. Mice were purchased from Charles River Laboratories and maintained under specific pathogen-free conditions. The housing facility was kept at 22°C (±2 °C) with a relative humidity of 30-70%. The light/dark cycle was 12h light/12h dark.

Ethics oversight

described in the method section:
The care and animal housing were in accordance with institutional guidelines and with the recommendations of the French Ethics

Committee (Comité Ethique en matière d' expérimentation animale de l'Institut Curie, National registration number: #118, authorization no.: 02163.02).

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