nature portfolio

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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	scRNAseq Data collection: STAR v2.4.2a Fluorescence micropscopy: ZEN Blue 3.3, Vectra Polaris™
Data analysis	scRNAseq Data analysis: R v3.6.2, R Studio 1.1.456, Seurat package v3, ggplot2 v3.3.2, InferCNV v1.2.1, ComplexHeatmap v2.2.0, python 3.7.6, pandas 1.0.1, numpy 1.18.1, matplotlib 3.2.2, CellChat 1.6.1 Image analysis: HALO® image analysis platform, PCR Data: Graphpad prism v8

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

Data availability statement:
Raw data are available at the European Genome-Phenome Archive (EGAS50000000365) and expression matrices are accessible at GEO (GSE254918).

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	Sex- and gender-based analysis was not performed. Biological samples from healthy donors or skin cancer patients from both sexes were collected
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	Biological samples from skin cancer patients (4mm punch biopsies) were collected only if the diameter of the tumor was large enough that the removal of a 4mm punch biopsy for scientific studies did not hinder histopathological evaluations. An experienced dermatopathologist selected the samples for sequencing after histopathological assessment. Healthy skin samples were collected from plastic surgeries of sun-protected abdominal or upper arm skin from Caucasian men and women aged 43 to 63 years.
Ethics oversight	Written informed patient consent was obtained before tissue collection in accordance with the Declaration of Helsinki. Our study was approved by the Institutional Review Board of the Medical University of Vienna under the ethical permits EK#1695/2021, EK#1783/2020 and EK#1555/2016.

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 size calculations were not performed. The sequencing data from n=10 tumors were validated in n=39 independent tumor samples with in situ stainings
Data exclusions	no data were excluded from the analysis
Replication	The sequencing data from n=10 tumors were validated in n=36 independent tumor samples with in situ stainings. In addition, our findings were confirmed in an entirely independent melanoma dataset (n=5; Werner et al., unpublished) and published datasets of oral SCC, cutaneous SCC and invasive BCC. In vitro experiments were repeated independently at least twice. All attempts of replication were successful.
Randomization	*Describe how samples/organisms/participants were allocated into experimental groups. If allocation was not random, describe how covariates were controlled OR if this is not relevant to your study, explain why.*
Blinding	Blinding was not possible as the histology reveals the tumor stage

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
[ ]	[ ] Palaeontology and archaeology
[ ]	[ ] Animals and other organisms
[ ]	[ ] Clinical data
[ ]	[ ] Dual use research of concern
[ ]	[ ] Plants

Methods

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

Antibodies

Antibodies used

Antibodies used for FACS: Fc blocking (1:500, CD16/CD32 BD #553142, RRID:AB_394656), CD45-BV605 (1:50, BioLegend #304042, RRID:AB_2562106), ITGA6-PeCy7 (1:100, BioLegend #313622, RRID:AB_2561705), CDH1-PeCy7 (1:200, BioLegend #147310, RRID:AB_2564188), FAP-APC (1:20, R&D Systems #FAB3715A, RRID:AB_2884010), CD90-AF700 (1:30, BioLegend #328120, RRID:AB_2203302) and CD31-FITC (1:30, BD Biosciences #563807), CD106-Pacific Blue (1:100, BD Biosciences #744309, RRID:AB_2742138), CD235ab-Pacific Blue (1:1000, BioLegend #306611, RRID:AB_2248153), CD4-FITC (1:400, [RPA-T4], BioLegend #300501, RRID:AB_314070), CD8-PE-Cy7 (1:100, [HIT8a] BD Biosciences Cat# 555635, RRID:AB_395997), CD25-APC (1:100, [BC96], BioLegend Cat# 302609 (also 302610), RRID:AB_314279), CD14-APC-Cy7 (1:100, [M5E2], BioLegend Cat# 301820 (also 301819), RRID:AB_493695), CD45RO-PacificBlue (1:100, [UCHL1], BioLegend Cat# 304215 (also 304216), RRID:AB_493658), CD127-PE (1:100, [A019D5], BioLegend Cat# 351340 (also 351303, 351304), RRID:AB_2564136), CD16-PerCP-Cy5.5 (1:500, [3G8], (BioLegend Cat# 302028 (also 302027), RRID:AB_893262).
Antibodies used for immunohistochemistry: Primary antibodies against CD90 (THY1) (1:200, rabbit monoclonal [EPR3133], Abcam #ab133350, RRID:AB_11155503), FAP (1:200, rabbit monoclonal [D3V8A], Cell signaling #13801, RRID:AB_2798316), TAGLN (1:12.000, rabbit polyclonal, Thermo Scientific #PA5-27463, RRID:AB_2544939), DES (1:2000, rabbit monoclonal [Y266], Abcam #ab32362, RRID:AB_731901), CD31 (1:500, rabbit, Neomarkers, #RB10333-P1)), CD3 (1:200, rabbit, Abcam #ab16669, RRID:AB_443425) and COL11A1 (1:200, rabbit polyclonal, Abcam #ab64883, RRID:AB_1140613) were diluted in 1%BSA/PBST and incubated over night. A biotinylated goat anti-rabbit antibody (1:200, Vector BA-1000) was used as second step.

Validation

Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

Melanoma cell lines (VM15, VM19, VM25, VM26, VM08): Berger, W., Hauptmann, E., Elbling, L., Vetterlein, M., Kokoschka, E.M., and Micksche, M. (1997). Possible role of the multidrug resistance-associated protein (MRP) in chemoresistance of human melanoma cells. Int. J. Cancer 71, 108–115. 10.1002/(SICI)1097-0215(19970328)71:1<108::AID-IJC18>3.0.CO;2-E.; SCC13: Lefort, K., Mandinova, A., Ostano, P., Kolev, V., Calpini, V., Kolfschoten, I., Devgan, V., Lieb, J., Raffoul, W., Hohl, D., et al. (2007). Notch1 is a p53 target gene involved in human keratinocyte tumor suppression through negative regulation of ROCK1/2 and MRCKα kinases. Genes Dev. 21, 562–577. 10.1101/gad.1484707.

Authentication

None of the cell lines were authenticated

Mycoplasma contamination

all cell lines tested negative for mycoplasma contamination

Commonly misidentified lines
(See ICLAC register)

n/a

Palaeontology and Archaeology

Specimen provenance

Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.

Specimen deposition

Indicate where the specimens have been deposited to permit free access by other researchers.

Dating methods

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

[ ] Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

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

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	*For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.*
Wild animals	*Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Reporting on sex	*Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.*
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJEguidelines for publication of clinical research and a completedCONSORT checklist must be included with all submissions.

Clinical trial registration	*Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.*
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links
May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session
(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

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	Fresh 4 mm punch biopsies from central tumor and unaffected skin adjacent to tumors as well as 10x10 cm healthy skin samples from abdominal plastic surgeries were subjected to cell isolation procedure directly after surgery. Healthy skin samples III-IV were cut into thin strips after removal of the fat layer. Epidermis was separated from dermis by Dispase 2 (1:100, Roche #04942078001, 20mg/mL), digested in PBS at 37°C for one hour before being peeled off. The epidermal sheet was minced and then subjected to enzymatic digestion in Trypsin-EDTA (GIBCO #25300-054) for 20 min at 37°C in a shaking water bath (Epidermal sheet protocol for enrichment of keratinocytes). Healthy skin dermis and tumor samples were cut into tiny pieces and digested with Collagenase 1 (1:100, GIBCO #17100-017, 50mg/mL), Collagenase 2 (1:100, GIBCO #17101-015, 50mg/mL), Collagenase 4 (1:100, Sigma-Aldrich #C5138, 50mg/mL), Hyaluronidase (1:100, Sigma-Aldrich #H3884, 10mg/mL) and DNAseI (1:250, Sigma-Aldrich #DN25, 5 mg/mL) in DMEM/10%FCS for one hour in a 37°C water bath (Protocol for enrichment of fibroblasts, keratinocytes and immune cells). After enzymatic digestion, the cell suspension was filtered and washed in PBS/10% FCS twice before subjecting it to FACS staining
Instrument	Aria Fusion, BD
Software	Diva, BD
Cell population abundance	Single cells were sorted into 384 well plates and were directly processed for sequencing. The purity was checked in due course of data analysis
Gating strategy	ITGA6+/CDH1+ keratinocytes, FAP+/CD90+ fibroblasts, CD45+ immune cells and FAP-CD90- double negative cells were single cell sorted directly into Smart-seq2 lysis buffer in 384-well plates. The gating strategy is shown in Suppl. Fig. 1A and 1B

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

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.