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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 Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Leica imaging software used to capture images of histological preps.
Data analysis	Software used: Abobe Illustrator CC 2017, Adobe Photoshop CC 2017, Prism6, DESeq2, GSNAP, Macs2, limma R package, QuSAGE, BETA, SDS 2.3.

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/reviewers upon request. 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

RNA-seq and ATAC-seq data supporting the findings of this study have been deposited in the Gene Expression Omnibus under accession number GSE116966. All other data supporting the findings of this study are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-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. Sample sizes were chosen to produce biologically meaningful data for comparison purposes.
Data exclusions	No data were excluded from the manuscript.
Replication	All attempts at replication were successful.
Randomization	As mice approached the age at which symptoms of BCC could expected, they were transferred to our vivarium where they were assigned one at a time into random treatment groups.
Blinding	Samples were blinded during data collection as follows. Treatment group was not noted until biological specimen had been analyzed.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	There are no restrictions on materials used in this study.

Antibodies

Antibodies used	Primary antibodies and their dilutions used in this study: Rabbit Sox9 1:300 (Millipore, AB5535), Rabbit Keratin1 1:1000 (Covance, PRB-165 [AF109]), Chicken Keratin5 1:2000 (Biolegend, 90501), Rabbit Keratin10 1:1000 (Biolegend, 90541), Rabbit Loricrin 1:1000 (Covance, PRB-145P), Goat IL-33 1:500 (R&D Systems, AF3626), Rabbit Ki67 1:500 (GeneTex, GTX16667 [SP6]), Rat BrdU 1:400 (BioRad, MCA2060) Rabbit CC3 1:400 (Cell Signaling, 9661), Human Ep-CAM undiluted (Ber-EP4; Ventana 760-4383). Rabbit Lhx2 1:400 (GeneTex,129241), Rabbit Gata6 Mab 1:400 (Cell Signaling, [D61E4], 5851S), Rabbit SCD1 Mab 1:1000 (Cell Signaling, [C12H5], 2794) Goat Klf5 1:100 (R&D Systems, AF3758). LRP6 antibody was produced in house and used at 30mg/kg. Secondary antibodies used in this study: anti-goat Cy3 (Jackson,705-166-147) anti-Rabbit Cy3 (Jackson, 711-166-152) anti-Rat Cy3 (Jackson, 712-166-153) Alexa Fluor 488 goat anti-rabbit A11008, Alexa fluor goat anti- chicken 488 A11039, Dako anti-Rabbit Envison+ System-HRP labelled polymer(K4003), Vectastain ABC kit (vector labs, PK4000).
Validation	We tested all antibodies by IHC and IF on mus musculus wildtype tissue to ensure the expected staining patterns.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Male and female Mus musculus of a mixed background harboring the correct alleles (BCC mice) were singly housed and

Laboratory animals	monitored for signs of significant advanced tumour burden, such as a scruffy coat and ear thickening which ususually occured around 8 weeks of age.
Wild animals	Study did not involve wild animals.
Field-collected samples	Study did not involve field-collected samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patients were 21 years of age or older, with new, operable, biopsy-confirmed, nodular BCC and willing to delay excision. Patients had adequate baseline hematologic function and hepatic function. Cases with histologic subtypes other than nodular BCC, Gorlin syndrome, prior treatment with any hedgehog pathway inhibitor, and pregnancy or lactation were excluded.
Recruitment	Patients seen in the clinic with a lesion that was appropriate were offered the opportunity to participate. Eligible patients with one target nodular BCC who were in conformance with the inclusion and exclusion criteria were eligible for enrollment. Confirmed new (not recurrent or previously treated or previously biopsied) nodular BCC at one of the listed anatomical sites, which must be biopsy confirmed at the study site (i.e., no outside biopsies)) Willingness to consent to biopsy of the lesion at baseline. Willingness to delay excision of the target tumor site until the time mandated in the protocol, unless evidence of disease progression or lack of drug tolerability.

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	Backskin was harvested from BCC mice harboring the Lgr5GFPDTR allele and processed into a single cell suspension. Cells were stained for CD34 and the live/dead marker SYTOX blue. GFP only tumor cells were collected.
Instrument	BD Biosciences Influx "jet-in-air" cell sorter equipped with a combination of 355, 405, 488, 561, and 640nm lasers.
Software	BDFACS Sortware 1.2.0.142
Cell population abundance	Of the live population, GFP+ cells accounted for approximately 6-10% of the population.
Gating strategy	Gating for low side scatter enriched for epidermal cells after dissociation of back skin samples. GFP negative animals were first processed to determine the GFP gate.

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