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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	Murine RNA-seq: FASTQC (v.0.11.2) Bowtie (version 2.2.3) Tophat (version 2.0.13) Cufflinks (version 2.2.1) PET-CT Reconstruction: OSEM3D, Inveon Research Workplace software Western blot data: Imagelab (v6.0.1) Flow cytometry: DIVA software qRT-PCR: SDS (v2.4)

Data analysis	Human transcriptome: LUMI Bioconductor package in R (v2.15.3) Murine RNA-seq: Cufflinks (version 2.2.1), CummeRBund (v.2.7.2) Pathway Analysis: GSEA: Broad institute GSEA (v2.0), Over-representation: Piano R package (version 1.8.2) Temporal expression patterning: MaSigPro R package (version 1.40.0) Pharmacogenomics: PharmacoGx package (version 1.1.6) qRT-PCR statistics: Relative Expression Software Tool (REST) (v1.22.2009) Flow cytometry Analysis: Flowjo (V10) Live cell imaging: Volocity (v6) Seahorse analysis: Wave (v2.6) Targeted metabolomics: Analyst (v1.6.3) Untargeted metabolomics: Mass Profiler Professional Graphical data presentation: Graphpad (v6)

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

GSE98157 for murine RNA-seq data and GSE98159 for human HT-12 array data.

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	Sample size calculation was performed for two independent samples (alpha = 0.05, power =0.8, mean difference of 10% for leg contracture)
Data exclusions	Methods section - Human sample collection and processing, Page 9 : Patients greater than 18 years of age planning to 10 undergo head and neck surgical procedures at the University Health Network between February 2015 to 11 July 2016 were screened for previous radiotherapy. Irradiated patients were included if they received full 12 dose radiotherapy to the neck (50-70Gy) for cancer therapy, were at least 150 days from completion of 13 treatment, and had a history and physical examination consistent with fibrosis. Patients treated with anti-fibrotic agents and those with fibrotic disorders were excluded.
Replication	The experimental findings were reliably reproduced through biological replicates and/or technical replicates.
Randomization	Animals were randomized into groups for treatment by a researcher blinded to treatment assignment.
Blinding	Outcome assessors were blinded when measuring functional and histologic changes to murine skin fibrosis severity.

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

Antibodies

Antibodies used

Western blot: Collagen-1 (ab138492, abcam, 1:5000), Fibronectin (ab2413, abcam, 1:5000), PAI-1 (sc5297, Santa Cruz, 1:1000), beta-actin (ab8229, abcam, 1:1000), PPARG (ab178860, abcam, 1:1000), ACOX1 (ab184032, abcam, 1:1000), Hexokinase 2 (ab104836, abcam, 1:1000), GFP (ab6556, Abcam, 1:1000), Rabbit-Cy3 (ab6939, Abcam, 1:2000).
Flow cytometry: CD36-PE (Human 336206, Biolegend) (Mouse 102605, Biolegend), CD31-PECy7 (102418, BioLegend), CD45-PECy7 (102418, BioLegend) .

Validation

All antibodies were obtained pre-validated and have been referenced. All antibodies used for western blots have been validated by the manufacturer and by references. Results from this manuscript were matched to the western blot profile supplied by the manufacturer. All flow cytometry antibodies were obtained from Biolegend specifically for flow cytometry application and have references on the manufacturer's website. Specifically for CD36, antibodies were also experimentally verified through CRPSIR/Cas9 knockout using two guide RNAs in human cells or by profiling CD36 KD mice. Please refer to manufacturer's website for a full list of references and for details regarding validation parameters by using the antibody number provided above. Sample references are found below.

Collagen-1: Wu X et al. CUG-binding protein 1 regulates HSC activation and liver fibrogenesis. Nat Commun 7:13498 (2016).

Fibronectin: Tang H et al. Loss of CLOCK under high glucose upregulates ROCK1-mediated endothelial to mesenchymal transition and aggravates plaque vulnerability. Atherosclerosis 275:58-67 (2018).
PAI-1: Wen et al. Hepatocyte Growth Factor Receptor Signaling Mediates the Anti-Fibrotic Action of 9-cis-Retinoic Acid in Glomerular Mesangial Cells. American Journal of Pathology 167:947-957 (2005).

Beta-Actin: Hall J et al. Evolution of a developmental mechanism: Species-specific regulation of the cell cycle and the timing of events during craniofacial osteogenesis. Dev Biol 385:380-95 (2014).

PPAR-G: Shen Y et al. Metabolic control of the scaffold protein TKS5 in tissue-invasive, proinflammatory T cells. Nat Immunol 18:1025-1034 (2017).

ACOX1: Zhang S et al. hsa-miR-29c-3p regulates biological function of colorectal cancer by targeting SPARC. Oncotarget 8:104508-104524 (2017).

HK2: Li Y et al. PDHA1 gene knockout in prostate cancer cells results in metabolic reprogramming towards greater glutamine dependence.Oncotarget 7:53837-53852 (2016)

GFP: Da Mesquita S et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature 560:185-191 (2018).

Animals and other organisms

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

Laboratory animals

All animal procedures were approved by Animal Care Committee at the University Health Network under AUP 3422. Female C3H/HeJ mice (Jackson Laboratory) or B6.129S1-Cd36tm1Mfe/J mice were obtained from Jackson Laboratory. All mice profiled in this manuscript were at 6-8 weeks of age.

Wild animals

This study did not involve wild animals.

Field-collected samples

This study did not involve field collected samples.

Human research participants

Policy information about studies involving human research participants

Population characteristics

This study was approved by the research ethics board at University Health Network (REB 15-9359-CE) and informed consent was obtained for each patient. Patients greater than 18 years of age planning to 10 undergo head and neck surgical procedures at the University Health Network between February 2015 to July 2016 were screened for previous radiotherapy. Irradiated patients were included if they received full dose radiotherapy to the neck (50-70Gy) for cancer therapy, were at least 150 days from

	completion of treatment, and had a history and physical examination consistent with fibrosis. Patients treated with anti- fibrotic agents and those with fibrotic disorders were excluded. Normal age matched control patients who were also undergoing head and neck surgical procedures were consented.
Recruitment	Patients were recruited by a research coordinator after screening for inclusion and exclusion criteria. Convenience sampling strategy was utilized.

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	Primary human dermal fibroblasts were treated with metabolic perturbation compounds and/or cytokines as per culture method conditions. Following this, cells were prepared for flow cytometry using antibodies as per manufacturer's instructions in terms of cell number per amount of antibody in FACS buffer (PBS + 1% FBS) and incubated for 30 minutes on ice. DAPI was added for identification of live cells.
Instrument	Analytical flow cytometry was performed on a Becton Dickinson LSRII flow cytometer
Software	Flowjo was used for analysis of flow cytometry data.
Cell population abundance	NA
Gating strategy	Compensation controls were performed when appropriate prior to flow analysis. Bulk of population was defined based on FSC-A/SSC-A. Doublets were removed based on FSC-W/FSC-H and SSC-W/SSC-H. Dead cells were gated out based on DAPI positivity. Following this, gating was performed on +ve populations of interest relative to unstained control or FMO control.

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