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Last updated by author(s): Jul 23, 2021

Reporting Summary

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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	NextSeq control software (v2.2.0, Illumina) was used for deep-sequencing of CRISPR screening and RNA-seq samples. NISElements (v4.4, Nikon) was used to acquire confocal IF microscopy images (Extended Data Fig 5a). Incucyte ZOOM/S3 control softwares (v2018a, ESSEN) were used to acquire microscopy images for all ADCP assays and drug titration assays. BD CSampler controller (v227, BD Biosciences) and BD FACSDiva (version 8.0, BD Biosciences) were used to acquire flow cytometry data.
Data analysis	Incucyte ZOOM or S3 software (v2018a, ESSEN) was used for automated microscopy analysis. CasTLE scripts (version 1.0, Morgens et al., 2016 Nature Biotech) were used for analysis of all screening data. For RNA sequencing analysis, transcripts were mapped using STAR v2.7.0 (Dobin et al 2013) and gene-level counts were generated using HTSeq v0.13.5 (Anders et al 2015), followed by differential gene expression analysis using DESeq2 v.1.28.1 (Love et al 2014). g:Profiler (version e.96_eg.43) was used to calculate gene ontology enrichments. Homology modeling was done as described in the Methods using SWISS-MODEL (template library SMTL version 2020-07-22, PDB release 2020-07-17), COOT (Version 0.7 (revision 4459)), FUGUE (Version 2.0) and REFMAC5 (Version 5.8.0135). Multicolor flow cytometry was analyzed with FlowJo (v. 10.6.1).

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

CRISPR screen and RNA-seq raw sequencing data are available under BioProject accession number PRJNA748551. All other primary data for all figures and supplementary figures are available from the corresponding author upon request. Gene dependency data from the Cancer Dependency Map is publicly available at www.depmap.org. Cancer expression data from TCGA (The Cancer Genome Atlas) is available at gdc.cancer.gov. CCLE data is available at https://sites.broadinstitute.org/ccle/.

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	For all CRISPR screens, experiments were performed in two replicates, based on the current standard in the field (e.g. Han et al., Nature 2020, Jeng et al., Cell Host and Microbe, 2019) and to optimize detection of robust and biologically meaningful hits. For mouse studies, sample sizes were determined based on previous experience with xenograft studies (e.g. Coles et al., Cancer Cell, 2020, Barkal et al., Nature 2019). For phagocytosis assays, sample sizes of 2-4 cell culture wells (usually 3-4) were chosen based on the literature (e.g. Barkal et al., Nature, 2019) and on preliminary experiments and sample sizes for each experiment are indicated in the legends. For RNA-seq, samples were prepared in triplicate based on the literature (e.g. Schafer et al., Nature 2017). For experiments with knockout cell lines, at least different 2 sgRNAs were used in in vitro assays to ensure that phenotypes were not an artifact of sgRNA off-target effects, following standards in the literature (e.g. Haney et al., 2018).
Data exclusions	No data were excluded.
Replication	Once experiments and procedures were fully optimized, all attempts at replication were successful. Screens were performed as two biological replicates. The genome-wide Ramos CRISPRko ADCP screen was also repeated independently a second time with two biological replicates, with largely similar results. Each mouse tumor experiment was performed once, as were full drug titrations in Extended Data Fig. 4i and Extended Data Fig. 10a,b, but effects of selected concentrations of GPR84 agonists were replicated independently. Otherwise unless indicated in legend, all experiments were performed independently at least two times.
Randomization	For mouse experiments, mice were randomly allocated into experimental groups. For other experiments including all in vitro assays, samples were necessarily allocated into groups based on their genotypes. Samples that were compared in in vitro assays were derived from the same parent cell line and thus differed only by the sequence of the guide RNA (i.e. control safe-locus-targeting, or gene-targeting) with which they were transduced.
Blinding	No blinding was performed. No blinding was performed in the in vitro assays, sequencing analysis of screens, or RNA-seq because all measurements and analysis were automated and thus prevented any bias. No blinding was performed in the mouse experiments as they were performed by individual investigators. For western blots, blinding was not possible because of clearly visible differences between conditions.

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 following antibodies were used: Mouse monoclonal anti-APMAP (Clone ID OTI4F6, cat. no. CF504220, Origene), mouse monoclonal anti-GAPDH (clone 6C5, cat. no. AM4300, Fisher), mouse monoclonal anti-FLAG (clone M2, cat. no. F1804, Sigma), rabbit polyclonal anti-beta actin (cat. no. ab8227, Abcam), rabbit polyclonal anti-calnexin (cat. no. ab22595, Abcam), mouse monoclonal anti-CD20-APC (clone 2H7, cat. no. 302309Biolegend), mouse monoclonal anti-CD47 (clone B6.H12, cat. no. BE0019-1, BioXCell), mouse monoclonal anti-Calreticulin-DyLight-488 (clone FMC 75, cat. no. ADI-SPA-601PE, Enzo Life Sciences), mouse monoclonal anti-TRP1 (clone TA99, cat. no. BE0151, BioXCell), recombinant human anti-CD2-APC (clone REA972, cat. no. 130-116-150, Mitenyi Biotech), recombinant human anti-CD30 (Clone Hu8, cat. no. MAB9576, R and D Systems), recombinant human anti-EGFR (clone Hu1, cat. no., MAB9577, R and D Systems), mouse/human chimeric monoclonal anti-CD20 antibody (with the constant region of the human IgG1 isotype and the variable region of rituximab; cat no. hcd20-mab1, Invivogen), rat monoclonal anti-CD45 (clone 30-F11, BV650-conjugated, cat. no. 103151, BioLegend), rat monoclonal anti-F4/80 (clone BM8, PE-conjugated, cat. no. 123109, BioLegend), and rat monoclonal anti-CD11b (clone M1/70, BV785-conjugated, cat. no. 101243, BioLegend). For mouse experiments, anti-CD20 (Rituxan) was from Stanford Pharmacy. Isotype controls were anti-B-Gal-hIgG1 (isotype control for hIgG1 in in vitro assays; cat. no. bgal-mab1, Invivogen), InVivoMAb mouse IgG2a isotype control, unknown specificity (isotype control for anti-TRP1 in mouse experiment, clone C1.18.4, cat. no. BE0085, BioXCell), InVivoMAb mouse IgG1 isotype control, unknown specificity (isotype control for mIgG1 in in vitro assays; clone MOPC-21, cat. no. BE0083, BioXCell).

Validation

APMAP antibody was validated by western blot using APMAP knockout cell lines. Mouse monoclonal anti-CD20-APC (Biolegend) was validated using CD20 knockout cell lines (Extended Data Fig. 4f). Mouse anti-CD47 (BioXCell) was validated using CD47 knockout Ramos cells (Extended Data Fig. 4g). Anti-CD20 (hcd20-mab1, Invivogen) was validated as active in phagocytosis susceptibility assays towards Ramos cells but not Ramos cells expressing guides targeting CD20/MS4A1 (Extended Data Fig. 1j).

See the following "Manufacturers Statement" for the other antibodies :

GAPDH mouse mAb (Fisher) recognizes endogenous levels of total human GAPDH protein. Monoclonal antibody is produced by immunizing animals with purified rabbit muscle GAPDH and is confirmed to be reactive towards human GAPDH. Reactivity has been confirmed on western blots with human SH-SY5Y and PC-3 cell lysates, and identifies the target band at ~37 kDa. Product Citations: Chalmers, Fiona, et al. "Inhibition of IRE1α-mediated XBP1 mRNA cleavage by XBP1 reveals a novel regulatory process during the unfolded protein response." Wellcome open research 2 (2017). Crummy, Ellen, et al. "The priming factor CAPS1 regulates dense-core vesicle acidification by interacting with rabconnectin3β/WDR7 in neuroendocrine cells." Journal of Biological Chemistry 294.24 (2019): 9402-9415.

Mouse monoclonal anti-TRP1 (clone TA99, BioXCell) has been extensively validated for in vivo triggering of FcyRs, e.g. Lehmann, B., et al. (2017). “Tumor location determines tissue-specific recruitment of tumor-associated macrophages and antibody-dependent immunotherapy response.” Sci Immunol 2(7): 10.1126/sciimmunol.aah6413.

Human anti-CD30 (Clone Hu8, cat. no. MAB9576, R and D Systems) was validated by the manufacturer using human Jurkat T cells.

recombinant human anti-CD2-APC (clone REA972, cat. no. 130-116-150, Mitenyi Biotech) was validated by the manufacturer using human peripheral blood mononuclear cells (PBMCs).

Recombinant human anti-EGFR (clone Hu1, cat. no., MAB9577, R and D Systems) was validated by the manufacturer using A431 human epithelial carcinoma cell line.

Beta actin rabbit polyclonal antibody (Abcam) recognizes endogenous levels of total human GAPDH protein. Polyclonal antibody is produced by immunizing animals with synthetic peptide (the amino acid sequence is considered to be commercially sensitive) within Human beta Actin aa 1-100. Reactivity has been confirmed on western blots with human HeLa and HEK293T cell lysates, and identifies the target band at ~42 kDa. Product Citations: Li Y et al. LncRNA-LET relieves hypoxia-induced injury in H9c2 cells through regulation of miR-138. J Cell Biochem 121:259-268 (2020). Xi X et al. MicroRNA-204-3p represses colon cancer cells proliferation, migration, and invasion by targeting HMGA2. J Cell Physiol 235:1330-1338 (2020). Jin Z et al. miR-330-3p suppresses liver cancer cell migration by targeting MAP2K1. Oncol Lett 18:314-320 (2019).

FLAG mouse mAb (Sigma) recognizes exogenously expressed FLAG-tagged proteins and has been extensively validated. The antibody recognizes the FLAG peptide sequence at the N-terminus, Met-N-terminus,C-terminus, and internal sites of the fusion protein. The immunogen was the FLAG peptide sequence (peptide sequence DYKDDDDK). Recent citations: ADAR2 regulates RNA stability by modifying access of decay-promoting RNA-binding proteins Aparna A Nucleic Acids Research 45(7), 4189-4201, (2017), MCPIP1, alias Regnase-1 binds and cleaves mRNA of C/EBP. Barbara Lipert PLoS ONE, (2017), HSV-2 glycoprotein gD targets the CC domain of tetherin and promotes tetherin degradation via lysosomal pathway Yalan Liu Virology , 154-154, (2016).

Rabbit polyclonal anti-calnexin (Abcam) detects endogenous levels of total human calnexin protein. The immunogen was synthetic peptide corresponding to Human Calnexin aa 550 to the C-terminus (C terminal) conjugated to keyhole limpet haemocyanin. The antibody has been validated for IF and has been validated by knockout. Recent product citations: Budge JD et al. Data for engineering lipid metabolism of Chinese hamster ovary (CHO) cells for enhanced recombinant protein production. Data Brief 29:105217 (2020), Chen JJ et al. DHHC5 Mediates ß-Adrenergic Signaling in Cardiomyocytes by Targeting Ga Proteins. Biophys J 118:826-835 (2020), Yang C et al. Exosomes of Antler Mesenchymal Stem Cells Improve Postoperative Cognitive Dysfunction in Cardiopulmonary Bypass Rats through Inhibiting the TLR2/TLR4 Signaling Pathway. Stem Cells Int 2020:2134565 (2020).
anti-

Mouse anti-calreticulin-DyLight-488 (Enzo Life Sciences) was produced in mice through immunization with purified calreticulin. This clone (FMC 75) has been used to detect cell surface calreticulin in the context of its presentation as a pro-phagocytic signal (Chao, Mark P., et al. "Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47." Science translational medicine 2.63 (2010): 63ra94-63ra94.) Other product citations: Inhibition of autophagy with chloroquine potentiates carfilzomib-induced apoptosis in myeloma cells in vitro and in vivo: V. Jarauta, et al.; Cancer Lett. 382, 1 (2016).

Rat anti-mouse CD45 antibody conjugated to Brilliant Violet 650 (BioLegend) was produced using mouse thymus or spleen as immunogen. This clone (30-F11) has been used to detect surface CD45. Recent product citations: Emgård J, et al. 2018. Immunity. 143:419.; Beura LK, et al. 2018. Immunity. 48:327.; Schulthess J et al. 2019. Immunity. 50(2):432-445.

Rat anti-mouse/human CD11b antibody conjugated to Brilliant Violet 785 (BioLegend) was produced in rat using mouse splenocytes as immunonge. This clone (M1/70) has been used to detect surface CD11b. Recent product references: Rhys HI, et al. 2018. EBioMedicine. 29:60.; Xi-Zhi J Guo et al. 2018. Immunity. 49(3):531-544.; Linehan JL et al. 2018. Cell. 172(4):784-796 .

Rat anti-mouse F4/80 antibody conjugated to PE (BioLegend) was produced in rat using murine macrophages as immunogen. This clone (BM8) has been used to detect surface F4/80. Recent product references: Michaud J, et al. 2017. BMC Microbiology . 10.1186/s12866-017-1036-0. Wang C, et al. 2017.; J Ethnopharmacol. 10.1016/j.jep.2017.06.014.; Liao Y, et al. 2017. Virol J. 10.1186/s12985-017-0801-x.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Ramos (cat. no. CRL-1596), K562 (cat. no. CCL-243), HeLa (cat. no. CCL-2), SKBR3 (cat. no. HTB-30), NCI-H23 (cat. no. CRL-5800), NCI-H82 (cat no. HTB-175), J774 (J77A.1, cat. no. TIB-67), B16-F10 (cat. no. CRL-6475), U-937 (cat no. CRL-1593.2), and 293T cells (cat. no. CRL-3216) (for lentivirus preparation) were from ATCC. Karpas-299 cells were from Sigma (cat no. 06072604). OVCAR8 was a gift from Amato Giaccia (Stanford). RKO and HCT-116 cells were a gift from Graham Casey (UVA). J774-Cas9 cells were a gift from Anita Sil (UCSF).
Authentication	Cell lines from ATCC were authenticated by the vendor using short tandem repeat (STR) profiling to distinguish between individual human cell lines and rule out intra-species contamination. No further authentication was performed.
Mycoplasma contamination	Cell lines were tested and confirmed negative for mycoplasma contamination by PCR.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	8-12 week old male and female NSG mice (Jackson Labs); 8-12 week old female C57BL/6 mice (Jackson Labs). Mice were group housed (3–5 mice per cage) with a 12-hour light/dark cycle (7am – 7pm), at 22°C ambient temperature and 40% humidity.
Wild animals	This study did not involve wild animals.
Field-collected samples	The study did not involve field-collected animals.
Ethics oversight	The Stanford Institute of Medicine Animal Care and Use Committee approved all animal studies and protocols.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	De-identified healthy male and female adult volunteer blood donors.
Recruitment	Recruitment of donors at SBC is based on hospital needs. Blood products for research are byproducts of normal donations, i.e. extra tubes of whole blood, white cells (buffy coats from whole blood and LRS chambers from apheresis).
Ethics oversight	The protocol was approved by the Stanford University Administrative Panel on Human Subjects in Medical Research. All donors provided informed consent.

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

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	For staining with single antibodies, cells were harvested by centrifugation, washed in PBS, and incubated with indicated antibodies at 4 deg C for 30 minutes, washed, and analyzed. For FACS screens, J774 cells were scraped following incubation with fluorescently-labeled Ramos target cells, washed in PBS, cryopreserved in aliquots, thawed, and filtered through a 40um filter prior to sorting over multiple sessions. In Extended Data Fig. 6j, tumor samples were mechanically diced and single cell suspensions were prepared, stained with Zombie NIR viability dye, fixed with paraformaldehyde, and stained with indicated antibodies.
Instrument	BD Accuri (Extended Data Figs. 2g,h, 4e,f,g,h,j,l, 9h) BD FACSAria II (Extended Data Fig. 9c), Novocyte Quanteon (Extended Data Fig. 6j).
Software	BD CSampler and BD FACSDiva were used to perform flow cytometry. FlowJo was used to create plots.
Cell population abundance	In the FACS macrophage screens, population abundance varied between the sub-library and genome-wide screens, and to a lesser extent between replicates. In pilot assays, high purity of sorted populations (i.e. appropriate calcein- and far-red-positivity/negativity) was confirmed by re-analysis on BD Accuri.
Gating strategy	For screens, live macrophages were gated based on FSC/SSC based on pilot experiments, and further gated on singlets. A four-way gate was set to not exclude any cells (to maximize the number of cells collected). For analysis of macrophage infiltration, cells were gated based on forward and side scatter, singlets were gated, live cells were gated based on lack of staining with Zombie-NIR dye, CD45+ cells were gated in order to separate the CD45+ and CD45- negative cells for each sample, and macrophages were gated as CD45+ cells that were positive for both CD11b and F4/80 (with a single macrophage gate applied to all samples, based on FMO controls).

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