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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	Imaging data were acquired by Dragonfly 200 Fusion (Andor) and FV3000 (Olympus). Flow Cytometry data were aacquired on Cytek Aurora. Proteomics data were collected using UltiMateTM 3000 RSLC nano system coupled to a Q-Exactive HF-X mass spectrometer (Thermo) (TMT) and Orbitrap Ascend mass spectrometer (DIA). Bioluminescence imaging was performed using the IVIS Spectrum 3D instrument (PerkinElmer). Scanning electron microscopy (SEM) images of migrasomes were acquired using a FEI Helios NanoLab G3 UC scanning electron microscope. Western blot images were scanned by ChemiDoc MP (Bio-Rad). Histopathological images of tissue sections were acquired using a digital pathology slide scanner (KF-PRO-120, KFBIO Co., Ltd.).
Data analysis	Image analysis was performed with Imaris 9.5.0 and Image J (Fiji). Statistical testing analysis was conducted by Graphpad Prism 9 and 10. Flow Cytometry data were analyzed by FlowJo™ (V10) Software. Proteomics data were analyzed using Spectronaut 15.6 software with default settings. Bioluminescence imaging data were analyzed using Living Image software (version 4.3.1, Caliper Life Sciences). Histopathological images of tissue sections were analyzed using K-Viewer (1.5.3.1).

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 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

All data associated with this study are present in the manuscript or its Supplementary Information files. Sequencing data and proteomics data from this study have been deposited at the China National Center for Bioinformation (CNCB) and will be publicly available from the date of publication. the accession numbers are CRA042049, HRA018134, OMIX016539, OMIX016540. 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	Sex and gender were not considered in this study and the information was not collected as part of our protocol.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, or other socially relevant groupings were not considered in this study.
Population characteristics	The human research participants are patients diagnosed with OSCC at Beijing Stomatological Hospital, or with breast cancer or lung cancer at West China Hospital, regardless of gender.
Recruitment	Human oral squamous cell carcinoma tissues were collected from OSCC patients, while blood samples were collected from breast or lung cancer patients. There is no self-selection bias.
Ethics oversight	The experiments involving human oral squamous cell carcinoma were approved by the Ethics Committee of the Institutional Review Board at Beijing Stomatological Hospital, Capital Medical University (approval number: CMUSH-IRB-KJ-PJ-2024-40). The use of blood samples from breast and lung cancer patients was approved by the Human Research Ethics Committee at West China Hospital of Sichuan University (permission number 2023 Review (no. 1546)).

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 statistical methods were used to predetermine sample sizes. Sample sizes were chosen based on our previous experience and standard practices in the field, and all exact n values are provided in the figure legends.
Data exclusions	No data were excluded from all other analysis.
Replication	All experimental findings were replicated successfully. Numbers of attempts of replication are described in the figure legends or Statistics and Reproducibility section of Method.
Randomization	Microscopic images were acquired randomized on any given samples. For in vivo experiments in mice, animals were randomized before treatment.
Blinding	The investigators were not blinded to allocation during experiments and outcome assessment.

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

Anti-CD41 antibody BD Bioscience Cat# 553847
Biotin anti-CD41 Biolegend Cat# 133930
Biotin anti-mouse Ter119 elabscience Cat# E-AB-F1125B
Biotin anti-human CD41 Biolegend Cat# 303734
Biotin anti-human CD235ab Biolegend Cat# 306618
Anti-mouse CD31 elabscience Cat# E-AB-F1180B
Anti-mouse CD45.2 elabscience Cat# E-AB-F1122B
Streptavidin-coated microbeads BEAVER Cat# 22308
Anti-Integrin α5 Cell signal Cat# 4705
Anti-CPQ Sigma Cat# HPA023235
Anti-NDST Santa Cruz Cat# sc-374529
Anti-PIGK Abcam Cat# ab201693
Anti-Integrin beta 1 Abcam Cat# ab179471
Anti-Calnexin Abcam Cat# ab20595
Anti-CD9 Abcam Cat# ab236630
Anti-Rab27a Cell signal Cat# 69295
Anti-GFP Abcam Cat# ab13970
Anti-Histone H3 HUABIO Cat# ET1701-64
Anti-Pigk Abcam Cat# ab201693
Anti-MHC class I abcam cat# ab134189 (WB)
Anti-MHC class I Invitrogen cat# 12-5998-81 (IF)
Anti-Eogt abcam cat# ab190693
Anti-Histone H3: Cell Signaling Tech cat# 4499S
Anti-CD63 abcam Cat# ab217345
Anti-Syntenin 1 Invitrogen cat# MA5-35685
Anti-Tsg101 abcam cat# ab125011
Anti-Kif23 Proteintech cat# 28587-1-AP
Anti-Flotillin-1 abcam Cat# ab41927
Rabbit Anti-Goat IgG(H+L)-HRP, SouthernBiotech, Cat# 6160-05
Goat Anti-Rat IgM mu chain (HRP), Abcam, Cat# ab98373
Goat Anti-Rabbit IgG (H+L), Jackson, Cat# 111-035-003
Goat Anti-Mouse IgG (H+L), Jackson, Cat# 115-035-003
Goat Anti-Rat IgG (H+L), Jackson, Cat# 112-035-003
Goat Anti-Mouse IgG(H+L), Proteintech, Cat# SA00001-1
Anti-mouse CD8 BioXCell Cat# BE0061
Rat IgG2b isotype control BioXcell Cat# BE0090
FITC anti-mouse CD69 Biolegend Cat# 104505
Brilliant Violet 605™ anti-mouse CD25 Biolegend Cat# 102036
Alexa Fluor@ 700 anti-mouse CD62L Biolegend Cat# 104426
Brilliant Violet 421™ anti-mouse CD8a Biolegend Cat# 100738
PE anti-mouse/human CD44 Biolegend Cat# 103007
FITC anti-mouse GranzB Invitrogen Cat# 11-8898-82

All primary antibodies used for western blotting were diluted at 1:2,000, and secondary antibodies at 1:5,000. All primary antibodies for immunofluorescence staining were diluted at 1:200, with secondary antibodies at 1:500. For flow cytometry, antibodies were used at the following dilutions: PE 1:600, APC 1:300, FITC 1:400, BV605 1:600, AF700 1:400, BV421 1:600. Flow cytometry antibodies used for imaging were diluted at 1:500. Antibodies for migrasome sorting were not used at a fixed dilution; the amount added was determined by the sample amount, as specified in the Methods section.

Validation

All antibodies were well validated commercial clones and routinely quality controlled by the manufacturer. Technical information could be found on the respective vendors' website by searching the catalog numbers provided above.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

The 4T1-luc (stable luciferase) and parental 4T1 cell lines were kindly provided by the laboratories of Professors Xin Lin

Cell line source(s)	(Tsinghua University) and Liufu Deng (Shanghai Jiao Tong University), respectively, and LLC cells were obtained from ATCC (CRL-1642).
Authentication	Identity of the cell lines were frequently checked by their morphological features and have been authenticated by the short tandem repeat (STR) profiling.
Mycoplasma contamination	All cell lines were tested to be mycoplasma-negative by the standard PCR method.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines are used in this study.

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	All C57BL/6J were purchased from animal center of Tsinghua University. All BALB/c and nude mice were purchased from Charles River and housed at the Tsinghua University and/or Zhejiang University Animal Center. Tspan4 KO mice were generated from GemPharmatech Co. Ltd. MMTV-PyMT mice were obtained from Dr. Hanqiu Zheng's lab in Tsinghua University. B2m-KO mice (Strain S-KO-01190) were purchased from Cyagen. Batf3-KO mice (C57BL/6J background) were a generous gift from the Li Wu laboratory at Tsinghua University. OT-I mice (C57BL/6J background) were a generous gift from the Hai Qi laboratory at Tsinghua University. 6-12 weeeks old male or female mice were used in the experiments.
Wild animals	None of the wild animals used.
Reporting on sex	This study did not involve sex based analyses.
Field-collected samples	This study did not involve samples collected from field.
Ethics oversight	All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) and conducted in accordance with governmental regulations and the guidelines of Tsinghua University and Zhejiang University for animal welfare (approval numbers 18-YL2, 22-YL2 and ZJU20250528).

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 ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	The experiments involving human oral squamous cell carcinoma were approved by the Ethics Committee of the Institutional Review Board at Beijing Stomatological Hospital, Capital Medical University (approval number: CMUSH-IRB-KJ-PJ-2024-40). The use of human blood samples was approved by the ethics committee on human research at the West China Hospital of Sichuan University (permission number 2023 Review (no. 1546)). Informed consent was obtained from the participants. No compensation was offered to any participant.
Study protocol	The trial protocol can be accessed from the Ethics Committee of the Institutional Review Board at Beijing Stomatological Hospital, Capital Medical University (approval number: CMUSH-IRB-KJ-PJ-2024-40), and the ethics committee on human research at the West China Hospital of Sichuan University (permission number 2023 Review (no. 1546)).
Data collection	OSCC cells were collected from the Human Oral Squamous Cell Carcinomas. Plasma samples (5–10 mL) were collected from cancer patients (EDTA-anticoagulated) after obtaining informed consent.
Outcomes	We isolated OSCC primary cells from the Human Oral Squamous Cell Carcinomas. We isolated tumor-derived migrasomes from the patient blood samples.

Plants

Seed stocks	No plants were used in this study.
Novel plant genotypes	No plants were used in this study.
Authentication	No plants were used in this study.

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	After co-incubation for the indicated times, cells were collected, blocked with Fc receptor blocker, and surface-stained with fluorophore-conjugated antibodies: FITC anti-mouse CD69 (clone H1.2F3, Cat# 104505, BioLegend), Brilliant Violet 605™ anti-mouse CD25 (clone PC61, Cat# 102036, BioLegend), Alexa Fluor® 700 anti-mouse CD62L (clone MEL-14, Cat# 104426, BioLegend), Brilliant Violet 421™ anti-mouse CD8a (clone 53-6.7, Cat# 100738, BioLegend), and PE anti-mouse/human CD44 (clone IM7, Cat# 103007, BioLegend). For intracellular granzyme B staining, cells were subsequently fixed and permeabilized using the Foxp3/Transcription Factor Staining Buffer Set (Invitrogen) and then stained with FITC anti-mouse Granzyme B (clone NGZB, Cat# 11-8898-82, Invitrogen). Viable cells were selected based on negative staining for the viability dye (eBioscience™ Fixable Viability Dye eFluor™ 780). Stained cells were acquired on a flow cytometer and analyzed with appropriate software.
Instrument	Data were analyzed on Cytek Aurora.
Software	FlowJo™ (V10) Software was used to analyze the data.
Cell population abundance	For the cell population, a customized gate was draw based on the control samples and applied to all other samples to obtain a population abundance for each samples.
Gating strategy	Single particles were gated on FSC/SSC, followed by gating a customized gate based on the control samples and applied to all other samples to obtain a population abundance for each samples.

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