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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 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	IncuCyte S3 Live-Cell Analysis System (Essen BioScience), Zeiss LSM710 laser microscope operated by MicroManager (ZEN2010B SP1; 6,0,0,485), CFX96 Touch Real-Time PCR Detection System operated by Bio-Rad iQ5 program.
Data analysis	Graphpad Prism (version 8.0.1), Image J software program (version 1.38x; National Institutes of Health), SPSS software (version 16.0), ClustalW2 algorithm, PyMOL Molecular Graphics System (Version 2.0 Schrödinger, LLC.), ESPript program (version 3.0).

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

The consensus caspase-8 recognition motifs were analyzed using CaspDB database (http://caspdb.sanfordburnham.org/). The p-Y705-Stat3-binding site in the GSDMC promoter was analyzed using the GPMiner program (http://gpminer.mbc.nctu.edu.tw/). All source data are reported as Source Data Tables for each figure and extended data figure in the supplementary information. All other data supporting the findings of this study are available from the corresponding author on reasonable request.

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 was determined based on published paper and previous experience. For in vitro studies, a sample size of n=3 would allow for adequate analysis to reach meaningful conclusions of the data. For in vivo studies, a bigger sample size (n=8 or 10) was used to compensate for the higher natural variance in vivo.
Data exclusions	No data were excluded from our analyses.
Replication	Our experimental findings were confirmed with at least 3 times independent experiments, unless otherwise indicated. All the experimental findings were reliably reproduced.
Randomization	All mice were randomly allocated into experimental groups. Standardized cell culture conditions (except for the intended experimental perturbation) were used to minimize variation across samples. All cells used throughout the study were differentially treated and analyzed in parallel to minimize experimental variation.
Blinding	IHC analysis was performed without any information about patient tissue. Blinding was used for animal works. For experiments other than IHC analysis and animal test, the investigators were blinded to group allocation during collection and/or analysis.

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 for immunoblotting at 1:1000: Rabbit anti-PD-L1 (Cat. #13684, clone #E1L3N), rabbit anti-cleaved caspase-8 (Cat. #9496, clone #18C8), rabbit anti-cleaved caspase-6 (Cat. #9761), rabbit anti-Phospho-Stat3 (Tyr705) (Cat. #9145S, clone #D3A7), and rabbit anti-lamin A/C (Cat. #2032T) from Cell Signaling Technology; Rabbit anti-GSDMC (Cat. #AP10771c, Abgent); Rabbit anti-GSDMC (Cat. #27630-1-AP, Proteintech); Mouse anti-Caspase-8 (Cat. #MAB704, clone #84131, R&D System); Mouse anti-Stat3 (Cat. #SC-8019, clone #F-2, Santa Cruz Biotechnology); Mouse anti-Flag (Cat. #F1804, clone #M2) and mouse anti-tubulin (Cat. #T5168, clone #B-5-1-2) from Sigma-Aldrich; Rabbit anti-HIF1α (Cat. #GTX127309, GeneTex). The following antibodies were used for immunoprecipitation at 1:100: Rabbit anti-PD-L1 (Cat. #13684, clone #E1L3N) and rabbit anti-Phospho-Stat3 (Tyr705) (Cat. #9145S, clone #D3A7) from Cell Signaling Technology. The following antibodies were used for immunofluorescence and Duolink assay at 1:200: Mouse anti-PD-L1 (Cat. #LS-C338364, clone #OTI2C7, LifeSpan BioSciences); Mouse anti-Flag (Cat. #F1804, clone #M2, Sigma-Aldrich); Rabbit anti-Phospho-Stat3 (Tyr705) (Cat. #9145S, clone #D3A7, Cell Signaling Technology). The following antibodies were used for immunohistochemical staining at 1:100--Rabbit anti-PD-L1 (Cat. #AB205921, clone #28-8, Abcam), Rabbit anti-HIF1α (Cat. #A300-286A, Bethyl Laboratories), Rabbit anti-Phospho-Stat3 (Tyr705) (Cat. #9145S, clone #D3A7, Cell Signaling Technology) and Rabbit anti-GSDMC (Cat. #GTX33979, GeneTex). The following antibodies were used for animal studies: Rat anti-TNFα (Cat. #BE0058, clone #XT3.11, at the dose of 300 μg/mouse) and rat anti-CSF1R (Cat. #BE0213, clone #AFS98, at the dose of 400 μg/mouse) from Bio X Cell.
Validation	All the anti-PD-L1 antibodies for immunoblotting, immunoprecipitation, immunofluorescence and Duolink assay, were validated by CRISPR/CAS9-based knockout in MDA-MB-231 and BT549 cells. Rabbit anti-PD-L1 antibody for immunohistochemistry: please see the manufacturer's website for references.

Rabbit anti-HIF1α antibody for immunoblotting was validated by ShRNA-based knockdown in HeLa cells.
Rabbit anti-HIF1α antibody for immunohistochemistry: please see the manufacturer's website for references.
Rabbit anti-cleaved caspase-8 and rabbit anti-cleaved caspase-6 antibodies for immunoblotting were validated by the treatment with inhibitors of active caspase-8 and -6. The similarity of molecular weight and immunoblotting patterns to that in manufacturer's website and published literatures was considered as secondary validation.
Rabbit anti-Phospho-Stat3 (Tyr705) for immunoblotting, immunoprecipitation, immunohistochemistry, and Duolink assay: please see the manufacturer's website for references.
Rabbit anti-lamin A/C for immunoblotting: please see the manufacturer's website for references.
Rabbit anti-GSDMC antibodies for immunoblotting were validated by CRISPR/CAS9-based knockout in MDA-MB-157 cells. Rabbit anti-GSDMC for immunohistochemistry was tested at a serial dilution in multiple human breast cancer samples, expected patterns of histological staining were observed in Figure 7g.
Mouse anti-Caspase-8 for immunoblotting was validated by CRISPR/CAS9-based knockout in MDA-MB-231 cells.
Mouse anti-Stat3 for immunoblotting: please see the manufacturer's website for references.
Mouse anti-Flag for immunofluorescence and immunoblotting: please see the manufacturer's website for references.
Mouse anti-tubulin for immunoblotting: please see the manufacturer's website for references.
Rat anti-TNFα for in vivo study: please see the manufacturer's website for references.
Rat anti-CSF1R for in vivo study: please see the manufacturer's website for references.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	MDA-MB-231, MDA-MB-157, 4T1, HEK293T, Hep3B, Tong, HA59T, SK-Hep-1, WRL68, HepG2, Huh7, Mahlavu, PLC, HA22T, H441, H820, HCC827, H358, H460, H226, H1993, PC-9, H322, H1650, H1299, H1395, H1435, H1355, T47D, ZR751, HOC-7, SB-2, Hs578T, BT549, MCF-7, and HeLa cells were obtained from ATCC.
Authentication	All cell lines used in this study were authenticated by short tandem repeat DNA finger printing.
Mycoplasma contamination	All cell lines used in this study were routinely tested for mycoplasma contamination and all tested negative for mycoplasma
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study

Animals and other organisms

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

Laboratory animals	Female 6- to 8-week-old BALB/c or BALB/c nude mice were purchased from The Jackson Laboratory. All animal procedures were conducted under the approval of the IACUC at MD Anderson
Wild animals	No wild animals were used in the study.
Field-collected samples	No field collected samples were used in the study
Ethics oversight	All animal procedures were conducted under guidelines approved by the Institutional Animal Care and Use Committee (IACUC) at MD Anderson Cancer Center.

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	The primary tumors of patients were diagnosed as breast cancer, including 1 male and 49 female, and the medium age was 59 year-old, and the treatments included surgical resection combined with chemotherapy. For the tumor represented in Figure 7g, female, 62 years old, breast cancer, stage 4.
Recruitment	Human breast tumor samples obtained from patients who underwent surgical resection at MD Anderson Cancer Center were reviewed by a pathologist and written informed consent was obtained from patients in all cases at the time of enrollment. All samples were collected with no bias.
Ethics oversight	The study design and use of paraffin-embedded human breast tumor samples were approved by the Institutional Review Board at MD Anderson Cancer Center.

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