

## 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

- |                                     |                                     |                                                                                                                                                                                                                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                           |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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 TOF-SIMS (IONTOF 5 GmbH, Münster, Germany), Imaging Mass Cytometry, Fluidigm's MCD Viewer software (v 1.0.560.2), Keyence Microscope software units commercially available

Data analysis Custom Python Codes. The analysis codes are available at <https://github.com/coskunlab/ScSpaMet> and also provided as a supplementary material. The IMC data was exported using MCD Viewer (v.1.0.560.2). Analysis used Anaconda (v. 4.12.0) and Jupyterlab (v. 3.2.8).

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](#)

Data availability

The IMC and 3D-SMF image data generated in this study have been deposited at <https://doi.org/10.5281/zenodo.6784251>. The mass spectrometry proteomics data

have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD045840. The metabolomic raw data have been deposited to MetaboLights with the dataset identifier MTBLS8685 ([www.ebi.ac.uk/metabolights/MTBLS8685](http://www.ebi.ac.uk/metabolights/MTBLS8685)). 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 was not considered in the study design. Sex of participants was determined based on self-report. No sex-based analyses was performed due to lack of female patient in tissue cores. |
| Reporting on race, ethnicity, or other socially relevant groupings | Race, Ethnicity, or other socially relevant groupings were not considered in the study design.                                                                                          |
| Population characteristics                                         | For lung tissue samples and tonsil samples, covariate-relevant population characteristics is provided in Supplementary Table 4-5.                                                       |
| Recruitment                                                        | <i>Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.</i>              |
| Ethics oversight                                                   | <i>Identify the organization(s) that approved the study protocol.</i>                                                                                                                   |

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](https://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     | 21 regions from tumor microarray, 11 regions from tonsil slides, and 5 regions from large endometrium slides.<br>No Statistical method was used to predetermine sample size.<br>Samples were collected until the sample size were sufficient to give comparison and reliable estimates. |
| Data exclusions | There are no data exclusions.                                                                                                                                                                                                                                                           |
| Replication     | At least 2 replicated per tissue from different imaging regions.                                                                                                                                                                                                                        |
| Randomization   | Not randomized. Covariates were not analyzed in our study. We are interested in spatial correlation of proteomic and metabolomic.                                                                                                                                                       |
| Blinding        | Not blinded. We are interested in spatial correlation of proteomic and metabolomic at the single cell level.                                                                                                                                                                            |

## 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                                  |
|-------------------------------------|--------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

### Antibodies used

Supplementary Table 2,3 and 4 shows the details of these antibodies CD20, CD3, CD4, CD45RO, CD68, CD8a, FoxP3, Pan-Keratin, Granzyme B, Ki-67, SMA, Collagen Ty1, E-cadherin, Histone 3, Vimentin, CD11b, CD44, CD31, CD45RA, CD11C, Intercaltor, CD38, BCL6, ICOS1, C-Myc, PD1, CD27, CD138, CXCR5, EZH2, CD21, CD86, CD83, CXCR4, H3K27ME3.

Antibodies were obtained from Standards Biotools:

EPR4106, D21H3, K112-91, D1K2T, EPR1344, Polyclonal, 236A/E7, ERP6855, H1, C8/144B, 9E10, ERP4877(2), B56, Poly, EPR8569

Antibodies were obtained from abcam:

EPR6454, EPR23463-30, EPR9307(2), EP3093, BU63, EPR23809-19, UMB2,

Antibodies were obtained from Cell Signaling technologies:

C36B11

### Validation

Antibodies were mostly obtained from Fluidigm as a validated immune panel. Additional validations were performed by immunohistochemistry (IHC) in tonsil formalin-fixed, paraffin-embedded (FFPE) sections. All antibodies were validated on human samples before and after metal isotope conjugation

## Plants

### Seed stocks

N/A

### Novel plant genotypes

N/A

### Authentication

N/A