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.

- 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
- 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
Sequencing data in Fastq Format was collected by various Illumina instruments using their proprietary algorithms

Data analysis
Reads are trimmed using fastx_trimmed (v 0.0.13)
Alignments are carried out using bwa mem (v. 0.7.15-r1140)
BedTools is used for calculating genome coverages (v.2.24.0)
samtools is used for downsampling sequence reads (v=1.3.1)
CNV analysis has been done using plasma seq (github.com/PeterUlz/PlasmaSeq)
ichorCNA is implemented as an R package and can be obtained at https://github.com/broadinstitute/ichorCNA.
R (version 4.0.2) and the ggpubr package (version 0.4.0)

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 following sequencing raw data sets have been deposited at the European Genome-phenome Archive (EGA; http://www.ebi.ac.uk/ega/) under the accession
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 sample size estimation has been performed, since this is an early pilot-study which is to demonstrate feasibility rather than discriminatory power of this analysis. This also means that we are unable to specify or estimate effect sizes |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | Data from two patients was excluded as detailed in the manuscript |
| Replication | Not applicable to this study |
| Randomization | No randomization has been performed |
| Blinding | No blinding has been performed. |

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 | Methods |
|---------------------------------|---------|
| n/a Involved in the study       | n/a Involved in the study |
| • Antibodies                   | • ChIP-seq |
| • Eukaryotic cell lines        | • Flow cytometry |
| • Palaeontology and archaeology| • MRI-based neuroimaging |
| • Clinical data                |          |
| • Dual use research of concern |          |

Antibodies

| Antibodies used | Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number. |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| Validation      | Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer’s website, relevant citations, antibody profiles in online databases, or data provided in the manuscript. |

Eukaryotic cell lines

Policy information about cell lines

| Cell line source(s) | State the source of each cell line used. |
|---------------------|------------------------------------------------------------------------------------------|
| Authentication      | Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated. |
| Mycoplasma contamination | Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination. |
| Commonly misidentified lines (See ICLAC register) | Name any commonly misidentified cell lines used in the study and provide a rationale for their use. |
Palaeontology and Archaeology

Specimen provenance

Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information).

Specimen deposition

Indicate where the specimens have been deposited to permit free access by other researchers.

Dating methods

If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

[ ] Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

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

Animals and other organisms

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

Laboratory animals

For laboratory animals, report species, strain, sex and age OR state that the study did not involve laboratory animals.

Wild animals

Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.

Field-collected samples

For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

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

We studied a cohort of 13 patients (DR1-DR13) with the inclusion criteria of metastasized CRC and progressive disease under one of the most widely used chemotherapies, i.e. FOLFOX. All relevant clinical data are summarized in the Supplementary Table 1

Recruitment

The study was approved by the Ethics Committee of the Medical University of Graz (approval number 26-288 ex 13/14 for the study part involving patients under FOLFOX treatment and 29-272 ex 16/17 for the collection and analysis of blood samples from healthy controls) conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients and healthy individuals, respectively. The patients were recruited in the Department of Internal Medicine Graz, Division of Oncology, Medical University of Graz, Graz, Austria; the healthy controls were recruited in the Department of Internal Medicine, Division of Hematology, Medical University of Graz, Graz, Austria

Ethics oversight

Ethics Committee of the Medical University of Graz

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

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:
No | Yes
---|---
☒ | Public health
☐ | National security
☒ | Crops and/or livestock
☐ | Ecosystems
☐ | Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No | Yes
---|---
☒ | Demonstrate how to render a vaccine ineffective
☒ | Confer resistance to therapeutically useful antibiotics or antiviral agents
☒ | Enhance the virulence of a pathogen or render a nonpathogen virulent
☒ | Increase transmissibility of a pathogen
☒ | Alter the host range of a pathogen
☐ | Enable evasion of diagnostic/detection modalities
☒ | Enable the weaponization of a biological agent or toxin
☒ | Any other potentially harmful combination of experiments and agents

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session

(e.g. UCSC)

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.
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
Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.

Instrument
Identify the instrument used for data collection, specifying make and model number.

Software
Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.

Cell population abundance
Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy
Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

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

Magnetic resonance imaging

Experimental design
- Design type
  Indicate task or resting state; event-related or block design.
- Design specifications
  Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.
- Behavioral performance measures
  State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition
- Imaging type(s)
  Specify: functional, structural, diffusion, perfusion.
- Field strength
  Specify in Tesla
- Sequence & imaging parameters
  Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.
- Area of acquisition
  State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.
- Diffusion MRI
  Used

Preprocessing
- Preprocessing software
  Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).
- Normalization
  If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.
- Normalization template
  Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.
- Noise and artifact removal
  Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).
### Volume censoring
Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

### Statistical modeling & inference

#### Model type and settings
Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

#### Effect(s) tested
Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

#### Specify type of analysis:
- [ ] Whole brain
- [ ] ROI-based
- [ ] Both

#### Statistic type for inference
(See Eklund et al. 2016)
Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

#### Correction
Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

### Models & analysis

| n/a | Involved in the study | Functional and/or effective connectivity | Graph analysis | Multivariate modeling and predictive analysis |
|-----|-----------------------|----------------------------------------|----------------|---------------------------------------------|
|     | [ ] Functional and/or effective connectivity | Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information). | Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.). | Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics. |
|     | [ ] Graph analysis | | | |
|     | [ ] Multivariate modeling or predictive analysis | | | |