***eLife’s* transparent reporting form**

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**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
* You should state the statistical method of sample size computation and any required assumptions
* If no explicit power analysis was used, you should describe how you decided what sample (replicate) size (number) to use

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

We did not formally compute the required sample size for this study. Instead, we determined it based on the availability, time and experience with comparable biological data yielding sufficient statistical power.

**Replicates**

* You should report how often each experiment was performed
* You should include a definition of biological versus technical replication
* The data obtained should be provided and sufficient information should be provided to indicate the number of independent biological and/or technical replicates
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* Criteria for exclusion/inclusion of data should be clearly stated
* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

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The number of replicates used can be found in the appropriate figure legends. Inclusion and exclusion of cells for scRNAseq analysis are indicated in the “Seurat preprocessing” methods section and quality control metrics are available in the supplemental data. scRNAseq datasets are available in open access on DRYAD at the following address: https://datadryad.org/stash/dataset/doi:10.5061/dryad.gf1vhhmrs?.

**Statistical reporting**

* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
* For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
* Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

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The statistical methods used can be found in the appropriate figure legends and in the methods for “Gene set enrichment analysis”

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
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* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
* Where provided, these should be in the most useful format, and they can be uploaded as “Source data” files linked to a main figure or table
* Include model definition files including the full list of parameters used
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Please indicate the figures or tables for which source data files have been provided:

scRNAseq datasets are available in open access on DRYAD at the following address: [https://datadryad.org/stash/dataset/doi:10.5061/dryad.gf1vhhmrs?](https://datadryad.org/stash/dataset/doi%3A10.5061/dryad.gf1vhhmrs).

The code that was used to generate the driver regulators is available at this address: <https://github.com/TajbakhshLab/DriverRegulators>. Any additional data is available from the corresponding author, S.T, upon request. Source data files have been provided for Figure 3J, Figure 4H, Figure 5F, Figure 5J, Figure 5-figure supplement 1E, Figure 7E and Figure 7G.