nature portfolio

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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	Single-cell libraries made using a chromium controller and Chromium Next GEM Single Cell 5' Reagent Kit, Version 2.0. Data sequenced using the Illumina NovaSeq 6000 platform for the capture of 70,000 reads/cell (50,000 for cDNA, 5,000 for TCR, 15,000 for the cell surface protein library)
Data analysis	Sequencing data was processed using CellRanger v6.1.2 and Souporcell, with clustering and PCA with cell phenotype calling performed using R Seurat v4.1.1. Batch correction was performed using harmony, and experimental doublets removed using a consensus of DoubletFinder, scDBLfinder, scDS. Visual and differential statistical analyses were performed using Visual Genomics Analysis Studio (VGAS). Statistical analysis of single-cell composition was performed using scCODA. Pathway analyses were performed using Enrichr, cell communication analyses using CellChat and LIANA, and common core pathway responsive gene analyses using PROGENy. CDR3 clonotypes were defined according to the IMGT database (www.imgt.org).

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 raw and normalized data generated by scRNA-TCR-CITE-sequencing and used in this study have been deposited to the NCBI Sequence Read Archive (PRJNA1070820) and GEO database under accession code GSE275871. The source data generated in this study both for main figures and supplementary figures are provided in the source data file with this paper. 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	Individuals of both sexes were included in our study and the ratio of males to females cited as a relevant biological construct in the description of the cohort in text. Data on gender was not collated from international cohorts and biorepositories for this study.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, or other social or sociopolitical constructs were not included in this study, and instead samples were pooled. We note in text that that patients varied in genetic race, but this was not specifically investigated in line with the global outcomes of this study across geographical populations.
Population characteristics	The VUMC cohort (US) and the AFRI-SCAR (South Africa) and AUS-SCAR (Australia) biorepositories which sourced the samples for this study all have a higher proportion of female patients, in line with the female predominance for this disease. There is otherwise limited global epidemiological data on SJS/TEN, which is estimated with an annual incidence of 1 to 5 per 1,000,000 patients.
Recruitment	patients are recruited to the different international cohorts and biorepositories through contact with specialist care centres i.e. the AUS-SCAR biorepository collects samples from all critical burn's centres across Australia. This close interaction also enables the collection of control skin and burn blister fluid as important 'healthy' and 'non-antigen-driven immunoinflammatory blister' comparators, respectively. Patients were selected for single-cell analysis based on the availability and cell yield and survival of samples and clinical background including information on the culprit drug for this study which was focused on small molecule drugs. This excluded samples from patients with SJS/TEN caused by large molecules including immune checkpoint inhibitors as they may represent a unique clinical phenotype and thus have been selected out as a potential source of experimental bias.
Ethics oversight	All samples including blister fluid and skin, clinical data, and analyses were obtained with informed consent under institutional review board (IRB) approval from Vanderbilt University Medical Center (IRB 131836, 150754, 171900), the University of Cape Town (HREC R031/2018, 500/2018), Austin Health (HREC 50791/Austin-2019), Murdoch University (HREC 2011/056, 2017/246, 2019/153), and the Western Australian Department of Health (RGS0000001924). All samples and data were de-identified.

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	We enrolled samples from 15 patients with small molecule drug-induced SJS/TEN including blister fluid (15 patients), and unaffected and affected skin (1 patient). We also included burn blister fluid (4 patients) and a healthy skin biopsy from an unrelated donor (1 donor). This represents one of the largest collections of patients with SJS/TEN generated to date due to the rare (1-5 per millions cases) incidence of disease. For blister fluids, a minimum of n>3 for both burn and SJS/TEN blister fluids were selected to enable statistical analysis of changes in single-cell composition using scCODA. For skin, as we cannot assume similar immunological time of reaction between patients, to delineate signatures of affected compared to unaffected tissue, we focused on time-paired analysis of samples from a clinically well-defined patient with unaffected skin, affected skin, and three blister fluids from distinct anatomical sites. Importantly, a minimum log-2-fold change, with FDR of 5% at 5000 genes and 1 million reads is possible with just 18 cells at 93% power. Further, to characterize a heterogeneous sample of 20 cell states, and sampling 50–100 cells/state, 1000 cells is statistically sufficient for de novo clustering. Individual samples from this patient had >1000 cells and we sequenced to a depth of 70,000reads/cell.

Data exclusions	No normalised data was excluded. Prior to normalization, cells with low (<500) UMI and cells with <100 genes and >50% mitochondrial content were removed to filter low-quality populations. A second filter used a defined mitochondrial-ribosomal RNA ratio of >0.47 to identify and remove apoptotic populations. Cells with >10% mitochondrial gene content were removed. Experimental doublets were identified and removed using a majority consensus benchmark of three independent bioinformatic algorithms (DoubletFinder, scDBLfinder, scDS). Subsets with <50 scRNA-defined cells were removed.
Replication	Identified TCR were confirmed by the SMART-seq plate-based assay in a subset of patients and replicates of the same samples were included in separate sequencing runs to ensure cell and TCR alignment between runs without batch variation. All attempts at replication were successful.
Randomization	Does not apply. This work does not describe an experimental study that requires allocation into groups
Blinding	Does not apply. This work does not describe an experimental study that requires allocation into groups

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
[ ]	[x] Antibodies
[x]	[ ] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[x]	[ ] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used	TotalSeq™-C Human Universal Cocktail, V1.0 (Biolegend, Cat. No. 399905) for single-cell CITE-sequencing as per manufacturer recommended (provided) concentration with 25µl of reconstituted antibody cocktail added to 25µl of FcR-blocked cells, and Ready-To-Use anti-CD8 (Cat. No. MM39-10; clone 144B, StatLab, McKinney, Tex), Ready-To-Use anti-CD103 (Cat. No. PA0374, clone EP206, Leica, Buffalo Grove, IL), and polyclonal anti-GNLY (Cat No. HPA058021, Atlas Antibodies, St. Louis, MO) at a dilution of 1:500 for immunohistochemistry.
Validation	These antibodies are commercially available, and specificity had been described and validated by the manufacturer for the TotalSeq™-C Human Universal Cocktail V1.0 (https://www.biolegend.com/en-gb/products/totalseq-c-human-universal-cocktail-v1-0-19736), anti-CD8 (https://www.statlab.com/mm39-10.html), anti-CD103 (https://shop.leicabiosystems.com/en-au/ihc-ish/ihc-primary-antibodies/pid-cd103) and anti-GNLY (https://www.atlasantibodies.com/products/primary-antibodies/triple-a-polyclonals/anti-gnly-antibody-hpa058021/).

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*