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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	Bacterial growth curve experiments were collected on a Tecan Group Ltd. Infinite Pro plate reader and a BioTek Synergy H1 microplate reader. Fluorescence measurements were measure using Tecan Group Ltd. Infinite Pro plate reader. Transepithelial water loss was measured using a Tewameter TM300 device (Courage & Khazaka Electronic GmbH). Electrophysiology experiments were performed using a 4-channel micro-electrode cavity array (100 µm MECA, Ionera Technologies) on an Orbit Mini (Nanion Technologies) system. Recordings were collected using the Elements Data Reader software, with parameters set to 200 pA gain and 1.25 kHz sampling rate and subsequently analyzed using the Elements Data Analyzer (v. 1.4.6).
Data analysis	Whole-genome sequencing, genome assembly, and annotation were conducted by SeqCenter facility (Pittsburgh, USA). blc2fastq (version 2.20.0.455) was used for quality control and adapter trimming for Illumina sequence reads. Porechop (version 0.2.3_seqan2.1.1) was used for quality control and adapter trimming for Nanopore sequence reads. Unicycler (version 0.5.0) was used to assemble Illumina and Nanopore reads. Bandage (version 0.8.1) and BUSCO (version 5.2.2) were used to assess assembly completeness. Genomes were annotated using Prokka (version 1.14.5). BAGEL4 (version 1.2) was used to detect biosynthetic gene clusters. Multi-locus sequence typing of genomes was performed using PubMLST (https://pubmlst.org). Gene cluster comparison and visualization were analyzed using CAGECAT (version 1.0). Multi-sequence alignments were analyzed and visualized using Geneious Prime (version 2024.0.7). Structural protein homology was analyzed and visualized using Foldseek (version 10) and PyMOL (version 3.0.3). All statistical analyses were performed with GraphPad Prism software (version 10.4.0).

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 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 data supporting the findings of this study are presented in the article, supplementary information, and source data file. Source data are provided with this paper. Reagents and strains created for this study are available upon request to the corresponding author.

The raw sequencing data have been deposited in the NCBI Sequence Read Archive under SRS24496481 [https://www.ncbi.nlm.nih.gov/sra/?term=SRS24496481] and SRS24496482 [https://www.ncbi.nlm.nih.gov/sra/?term=SRS24496482]. The nucleotide sequencing data for S. hominis AH5011 and S. aureus AH6350 have been deposited in the National Center for Biotechnology Information (NCBI) GenBank under BioProject PRJNA1222585 and accession codes JBLOOY000000000 [https://www.ncbi.nlm.nih.gov/nuccore/JBLOOY000000000.1] and CP183426 [https://www.ncbi.nlm.nih.gov/nuccore/CP183426]. The genomes used in this study are listed in Supplementary Table 3 and are provided below:
JALGOD010000000 [https://www.ncbi.nlm.nih.gov/nuccore/JALGOD000000000.1]
DAPATD010000000 [https://www.ncbi.nlm.nih.gov/nuccore/DAPATD000000000.1]
BEBO01000000 [https://www.ncbi.nlm.nih.gov/nuccore/BEBO00000000.1]
JAHCOD000000000 [https://www.ncbi.nlm.nih.gov/nuccore/JAHCOD000000000]
JAESMK010000000 [https://www.ncbi.nlm.nih.gov/nuccore/JAESMK000000000.1]
NZ_CP134841 [https://www.ncbi.nlm.nih.gov/nuccore/NZ_CP134841]
QVTZ01000000 [https://www.ncbi.nlm.nih.gov/nuccore/QVTZ00000000.1]
QKXS01000000 [https://www.ncbi.nlm.nih.gov/nuccore/QKXS00000000.1]
JAHNUV000000000 [https://www.ncbi.nlm.nih.gov/nuccore/JAHNUV000000000]
JARAAJ000000000 [https://www.ncbi.nlm.nih.gov/nuccore/JARAAJ000000000]
DAGYEO010000000 [https://www.ncbi.nlm.nih.gov/nuccore/DAGYEO000000000.1]
CAJESU010000000 [https://www.ncbi.nlm.nih.gov/nuccore/CAJESU000000000.1]
PZFH01000000 [https://www.ncbi.nlm.nih.gov/nuccore/PZFH00000000.1]
PZEZ01000000 [https://www.ncbi.nlm.nih.gov/nuccore/PZEZ00000000.1]

The mass spectrometry data have been deposited in the Zenodo database. Links to the deposited data can be found here: Hominicin LC-MS Quantification [https://zenodo.org/records/14834706], S. hominis spent media LC-MS and MS/MS [https://zenodo.org/records/14833876], Staphylococci Knockout LC-MS Screening [https://zenodo.org/records/14834696], and Staphylococci Knockout Screening 2 LC-MS [https://zenodo.org/records/16877503].

The NMR data have been deposited in the Natural Products Magnetic Resonance Database (NP-MRD) under project code NP0350779 [https://doi.org/10.57994/3763].

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	In this study, only bacterial isolates were used. These isolates were obtained from previously published collections, as referenced in the Methods section (Nakatsuji et al., Sci Transl Med, 2017; Cau et al., J Allergy Clin Immunol, 2021). Participants included individuals of both sexes, who had not used antibiotic in the preceding month. Sex and/or gender of participants were self-reported. Informed consent was obtained from all 59 healthy participants and 42 patients with atopic dermatitis. UCSD participants were 54% male and 46% female. For procedures involving whole-human blood, samples were collected from 3 healthy adult donors (1 male and 2 females). Informed consent was obtained from all subjects prior to participation. Disaggregated sex data is provided in the source data file.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, or other socially relevant groupings are not relevant in this study. Participants of all ethnicities were recruited.
Population characteristics	Not applicable to this study
Recruitment	In this study, only bacterial isolates were used. These isolates were obtained from previously published collections, as referenced in the Methods section (Nakatsuji et al., Sci Transl Med, 2017; Cau et al., J Allergy Clin Immunol, 2021). In case of blood donations, individuals currently taking NSAID painkillers or anti-coagulant drugs, as well as participants weighting <80 pounds, were excluded. Healthy adult members of the Anschutz Campus community (both sexes, all ethnicities, non-pregnant) were recruited as the donors. No identifiable health information were collected in this study.
Ethics oversight	Ethics oversight is provided in the manuscript. Skin swab collection was done in accordance with protocols approved by the University of California, San Diego (UCSD) Institutional Review Board under project number 140144. Bacterial isolates from skin swabs of healthy subjects were collected in accordance with protocols approved by Colorado Multiple Institutional Review Board under protocol number 19-2218 and UCSD Institutional Review Board under project number 071032.

All procedures involving human blood samples were conducted in accordance with guidelines approved by the Colorado Multiple Institutional Review Board (COMIRB) under protocol number 17-1926 and the Institutional Biosafety Committee under protocol number IBC-00001264.

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	Power calculations are performed using the Normal Power Calculations application for two-sided alternative hypothesis UCLA Statistics Online Calculator (http://calculators.stat.ucla.edu/powercalc/normal/n-1/n-1-samp.php) to determine the number of animals required to observe a 50% change in virulence, as assessed by T-test or Chi-squared analysis of bacterial colony counts or mortality (LD50), given an expected experimental variance within a treatment group of up to 20%. From this, at least ten mice per treatment group is sufficient. For all other in vitro experiments, no statistical methods were used to determine sample sizes. The sample sizes were determined based on literature reporting similar experiments (e.g., Severn et al., mBio, 2022, doi: 10.1128/mbio.00930-22; Rutter et al., Nat Commun, 2024, doi: 10.1038/s41467-024-50591-8; Zipperer and Konnerth et al., Nature, 2016, doi:10.1038/nature18634; Puls et al., ISME J, 2024, doi:10.1093/ismejo/wrae044).
Data exclusions	No data was excluded from analysis.
Replication	We confirm that all replication attempts were successful. Unless otherwise stated in the figure legend, each experiment was conducted in biological triplicate, with each biological triplicate in technical duplicate or triplicate.
Randomization	To ensure balanced representation, an equal number of 8-week-old five males and five female C57BL6/J mice were allocated to each experimental group based on age and sex. Randomization was not applied, as mice were matched for age and sex during group assignment to minimize confounding variables. No additional covariates were relevant to this study.
Blinding	All disease score analyses from digital photographs of the mouse skin were performed in a blinded manner. Photographs were captured under standard lighting and imaging conditions. Images were randomized to conceal treatment group and sex prior to scoring. Independent evaluators, unaware of the experimental conditions, provided individual grades for erythema, edema, erosion and scaling. Other experiments were not blindly performed as the results were obtained directly by instrument measurements.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Immortalized human N/TERT-2G keratinocytes were generously gifted and sourced by Dr. James Rheinwald laboratory. The cell line was sourced from a male newborn individual. The primary literature to the cell line can be found in PMID: 10648628, doi: 10.1128/mcb.20.4.1436-1447.2000

Authentication	Not applicable for this study. The N/TERT-2G keratinocytes used in this study were obtained as gifts from the original source of the cell line (Rheinwald laboratory). The cell line was not authenticated in-house.
Mycoplasma contamination	We confirm that immortalized N/TERT keratinocytes used in this study are tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	We confirm that the cell line N/TERT-2G keratinocytes (Cellosaurus Accession CVCL_UZ62) are not listed in the database of known misidentified cell lines.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Eight-week-old male and female C57BL6/J mice (strain #000664) were obtained from the Jackson Laboratory and housed in specific pathogen-free facilities at the University of Colorado Anschutz Medical Campus Animal Care Facility under controlled conditions (12-hour light/dark cycle; temperature: 20-22ºC; humidity: 30-70%). Mice were provided ad libitum access to food and water and allowed to acclimate for 1 week prior to experimentation. At experimental endpoints, mice were euthanized via CO2 inhalation followed by cervical dislocation. This method is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals. Species: Mus musculus Strain/substrain: C57BL/6J (strain #000664) Genetic background: inbred Age of experimentation: 8 weeks Sex: Both male and female Source: The Jackson Laboratory (Bar Harbor, ME, USA)
Wild animals	Not applicable to this study.
Reporting on sex	Sex was considered in the study design; therefore, we used an equal number of five male and five female C57BL6/J mice for each condition tested.
Field-collected samples	Not applicable to this study.
Ethics oversight	All vertebrate animal experiments were approved and conducted in accordance with the Institutional Animal Care and Use Committee of the University of Colorado Anschutz Medical Campus under protocol number 00941.

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

Plants

Seed stocks	Not applicable to this study.
Novel plant genotypes	Not applicable to this study.
Authentication	Not applicable to this study.