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	Thermo Scientific Smart EPU Software combined with MotionCor2
Data analysis	Gene sequences were analyzed in SnapGene software. Cryo-EM data processing was conducted in cryoSPARC (version 3.1), and subsequent model building and refinement was accomplished with ChimeraX_Daily, Coot (version 0.9.8.7), and Phenix (version 1.20.1). Dose-response curves were prepared using GraphPad Prism (ver. 11.0.0).

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

The cryo-EM density maps for NKA-, EB1001-, EB1002-, 336-, and 383-bound NK2R-Gq complexes have been deposited in the Electron Microscopy Data Bank (EMDB) under accession code EMDB-65549, EMDB-65570, EMDB-65571, EMDB-65572, and EMDB-65573, respectively. Atomic coordinates for the atomic models

of NKA-, EB1001-, EB1002-, 336-, and 383-bound NK2R-Gq complexes have been deposited in the Protein Data Bank (PDB) under the accession numbers 9W1J, 9W2G, 9W2H, 9W2I, and 9W2J, respectively.

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	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	For cryo-EM data collection, no methods were used to predetermine sample size. The size of the cyro-EM datasets was determined by the need to sufficiently identify proteins and generate high-resolution maps and atomic models, and was based on previous experience. The number of micrographs and particles were listed in the Extended Data.
Data exclusions	Micrographs with low resolution estimates following CTF fitting were discarded. The algorithms used for cryo-EM image processing may exclude unsatisfying particles based on their refinement strategy. And no other data were excluded.
Replication	Pharmacological curves were reproduced in biological triplicate.
Randomization	For calculation of the Fourier Shell Correlation (FSC), cryo-EM particles were randomly split into two halves.
Blinding	N/A

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

Antibodies

Antibodies used	Monoclonal mouse anti-FLAG M1 antibody (Sigma-Aldrich, Cat#F3040) was used for NK2R protein purification.
Validation	Mouse anti-FLAG M1 antibody was validated in the lab by testing against protein standards harboring the epitope tag.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Expi293F human cells (Thermo Fisher Scientific), COS-7 green monkey kidney fibroblast-like cell line (ATTC)
Authentication	Cell lines were purchased directly from the vendor and thus were not authenticated at the Univeristy of Copenhagen.
Mycoplasma contamination	All cells lines regularly tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	N/A

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A