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Life Sciences Reporting Summary

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For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Experimental design

1. Sample size

Describe how sample size was determined.

We used a power calculation (80% power, 0.05 type I error) to see an 3 to 5-fold effect in vivo (depending on data distribution), which was an n =10.

2. Data exclusions

Describe any data exclusions.

No data were excluded

3. Replication

Describe the measures taken to verify the reproducibility of the experimental findings.

All cell culture experiments were repeated three independent times. In vivo experiments were performed by multiple laboratory members again with independent repeat experiments. Binding data (SPR and ELISA) were performed by different laboratories and achieved the same result.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

Not randomized. There was no need to randomized animals for this study. However, the animals were purchased commercially, age- and sex-matched.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Not blinded. Although the study was not blinded, key experiments were repeated independently by multiple members of the laboratory

Note: all in vivo studies must report how sample size was determined and whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ 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 any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ Test values indicating whether an effect is present *Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes noted.*
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars in all relevant figure captions (with explicit mention of central tendency and variation)

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	GraphPad Prism 7.0 FASTX-Toolkit 0.0.13 (http://hannonlab.cshl.edu/fastx_toolkit/) cutadapt 1.8.1 MAGeCK 0.5.4 FlowJo X 10.0.7 BIAevaluation 3.1 PyMOL: v1.7.6.4

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a third party.	There are no restrictions. These will be available by MTA.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Anti-Mxra8 antibodies were validated by Western blotting, binding to recombinant protein, and binding to transfected cells. Antiviral antibodies have been published previously and validated by FACS with infected cells.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	MEFs were generated from C57BL/6 mouse embryos (Diamond laboratorty). Vero, NIH-3T3, HEK 293T, A549, HeLa, and HFF-1 were purchased from ATCC, Hs 633T was purchased from Sigma-Aldrich (#89050201), Huh7 were provided by the Rice Laboratory, RPE were provided by M. Mahjoub, Washington University), JEG3 were provided by the Mysorekar laboratory (Washington University). U2OS cells were provided by the Cherry Laboratory (University of Pennsylvania). Primary human keratinocytes (KE, #102-05n), synovial fibroblasts (SF, #408-05a), osteoblasts (OB, #406-05f), chondrocytes (CH, #402-05f), and skeletal muscle cells (SMC, #S150-05f) were purchased from Cell Applications. Primary human dermal fibroblasts (DF, #CC-2509) were obtained from Lonza. Additional cell lines used were HTR8/SV (provided by I. Mysorekar, Washington University), MRC5 (provided by D. Wang, Washington University), hCMEC/D3 (provided by R. Klein, Washington University), Jurkat (ATCC), Raji (ATCC), K562 (ATCC), HT1080 provided by J. Cooper, Washington University), and Hs 633T (#89050201, Sigma-Aldrich).
b. Describe the method of cell line authentication used.	None
c. Report whether the cell lines were tested for mycoplasma contamination.	All cell lines were tested and judged free of mycoplasma contamination using a commercial kit. Primary cells were not tested
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	None

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide all relevant details on animals and/or animal-derived materials used in the study.

Experiments were carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health after approval by the Institutional Animal Care and Use Committee at the Washington University School of Medicine. We used C57BL/6, wild-type, male, four-week-old mice purchased from Jax,

Mxra8-Fc or an IgG control (JEV-13 mAb) (250 µg per mouse in PBS) was administered to four week-old WT male C57BL/6 mice 6 h prior to subcutaneous inoculation in the footpad with CHIKV-AF15561. Alternatively, in co-injection experiments, CHIKV or ONNV was mixed directly with Mxra8-Fc or JEV-13 and incubated at 37oC for 30 min before inoculation. At 12 h, 24 h, and 72 h post infection, animals were euthanized, and after perfusion with PBS, tissues were harvested. For antibody pre- or post-treatment experiments, 300 µg of purified hamster mAbs 1G11.E6 + 7F1.D8, 4E7.D10 + 8F7.E1, and isotype control PIP (Bio X cell # BE0260) in PBS were administered via an intraperitoneal route to four week-old WT male C57BL/6 mice 12 h prior or 8 or 24 h post subcutaneous inoculation in the footpad with CHIKV AF15561. Joint swelling was monitored at 72 h post infection via left foot measurements (width x height) using digital calipers.

The Armenian hamsters were purchased from Cytogen Research and Development, Cambridge, MA. There is no substrain. We used male animals. The animals were approximately 7 months old at the time of fusion (fused in August 2017, arrived at WU in March 17 approx 8 weeks old).

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

No human studies