

Two competing HUSH complexes orchestrate retroelement immunity

Joshua Miguel C. Danac^{1,2}, Rachael E. Matthews^{1,2}, Akhila Gungi^{1,2}, Chuyan Qin^{1,2}, Harriet Parsons³, Robin Antrobus³, Richard T. Timms⁴, and Iva A. Tchasovnikarova^{1,2}

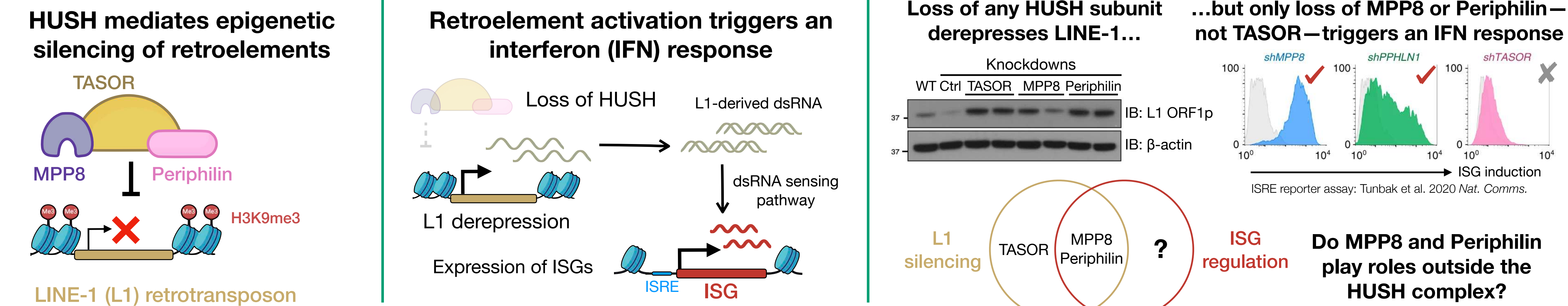
¹Gurdon Institute, University of Cambridge ²Department of Biochemistry, University of Cambridge ³Cambridge Institute for Medical Research, University of Cambridge ⁴Cambridge Institute of Therapeutic Immunology and Infectious Disease, Jeffrey Cheah Biomedical Centre, University of Cambridge.

✉ jmc3@cam.ac.uk

KEY POINTS

- The TASOR paralog TASOR2 forms the HUSH2 complex with MPP8 and Periphilin
- Whereas HUSH silences retroelements, HUSH2 is recruited by IRF2 to repress interferon-stimulated genes (ISGs)
- HUSH and HUSH2 compete for their shared subunits MPP8 and Periphilin
- HUSH-HUSH2 competition couples ISG induction to retroelement silencing

BACKGROUND



RESULTS

1 TASOR2 forms the HUSH2 complex

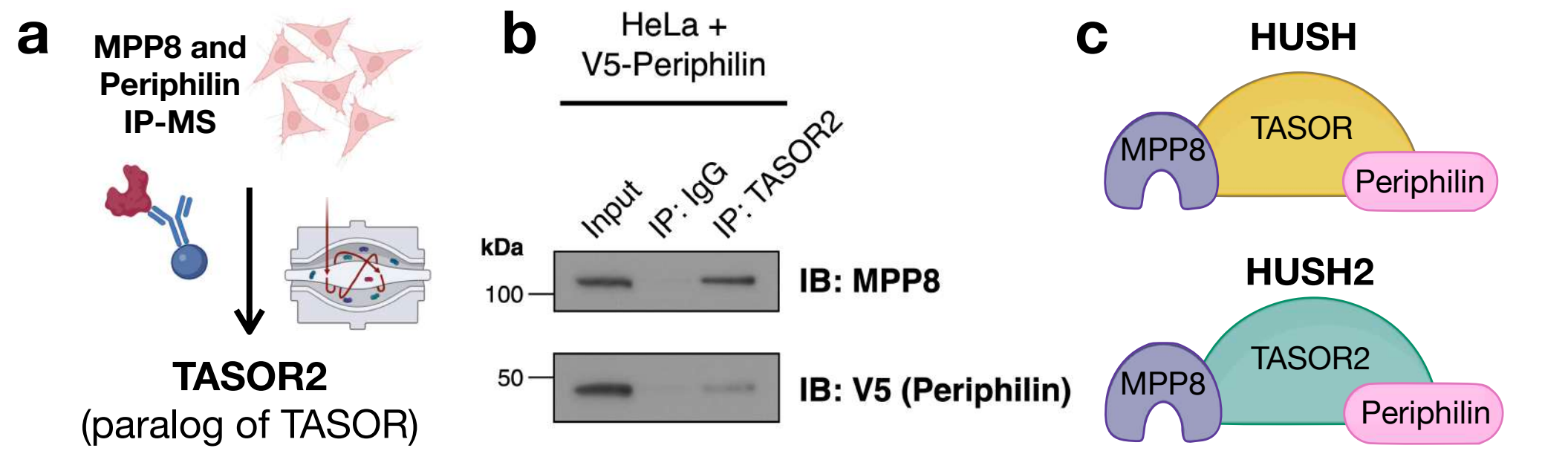


Fig. 1. Proteomic screens for MPP8 and Periphilin interactors identified TASOR2 (a), which also binds to MPP8 and Periphilin (b), forming a paralogous HUSH2 complex (c).

2 Loss of HUSH2, but not TASOR, upregulates ISGs

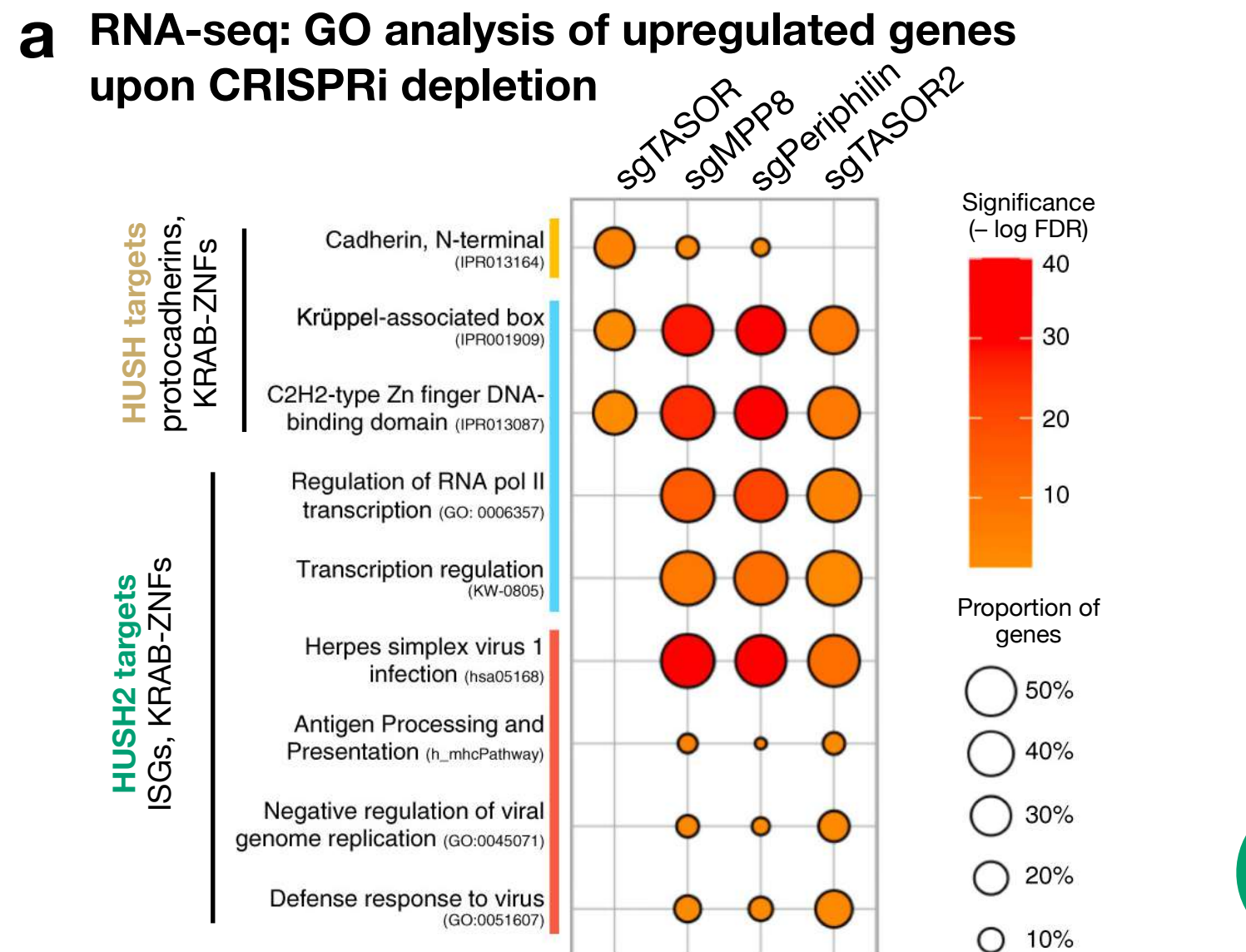


Fig. 2. TASOR and TASOR2 regulate distinct transcriptional targets shared with MPP8 and Periphilin (a). The loss of HUSH2, but not TASOR specifically up-regulates the expression of ISGs and MHC class I (b).

Read the full paper here:
Danac et al. 2024 *Molecular Cell*.
Competition between two HUSH complexes orchestrates the immune response to retroelement invasion.

3 HUSH2 binds promoters of ISGs & KRAB-ZNFs

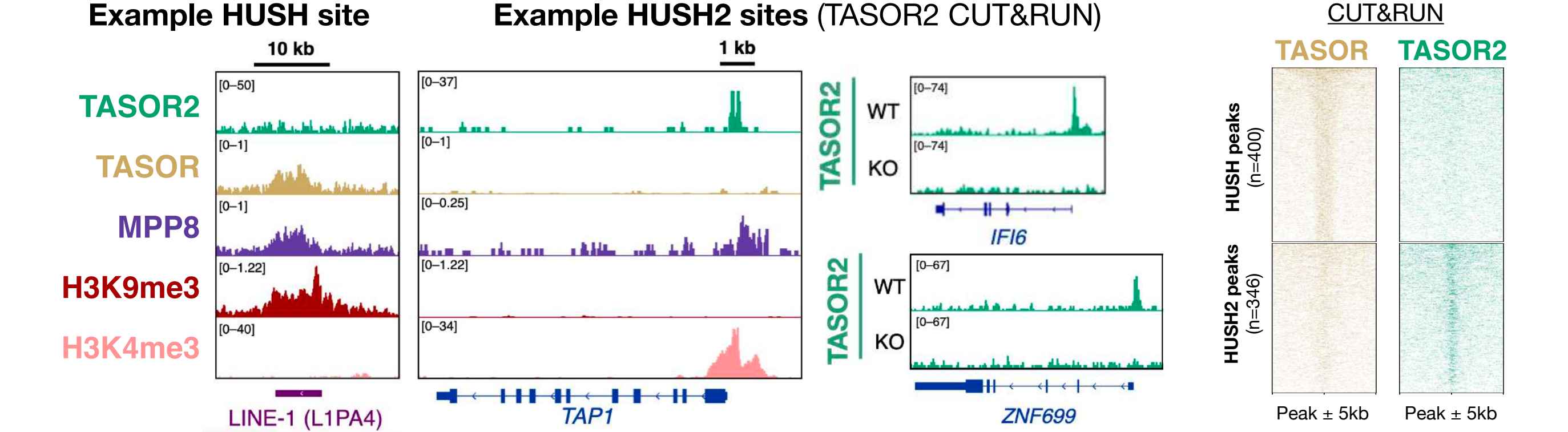


Fig. 3. CUT&RUN for TASOR2 revealed that HUSH and HUSH2 bind distinct and mutually exclusive genomic targets, with HUSH2 occupying the promoters of ISGs and KRAB-ZNF genes. TASOR, MPP8, and H3K9me3 ChIP-seq: Liu et al. 2019 *Nature*. H3K4me3 ChIP-seq: ENCODE.

4 IRF2 recruits HUSH2 to repress ISG expression

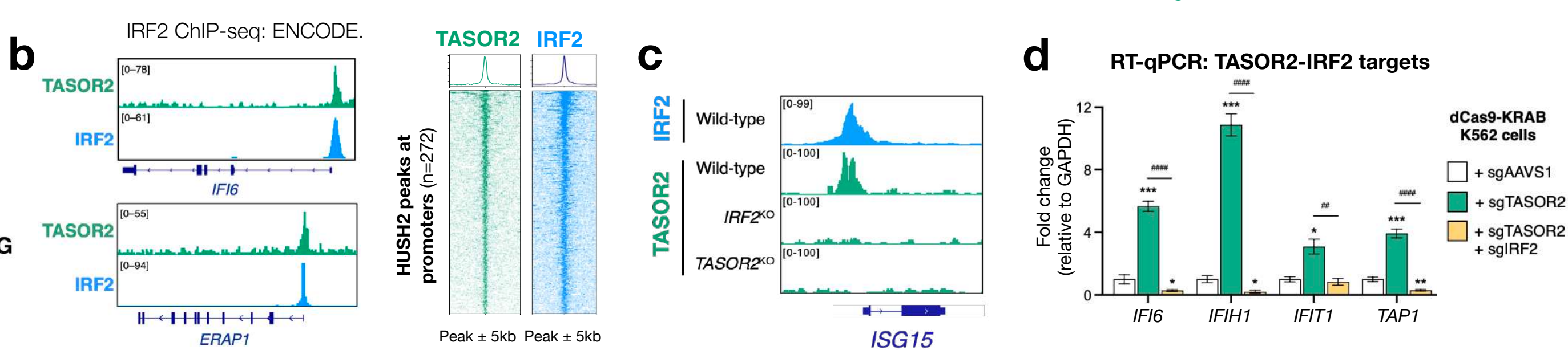


Fig. 4. Transcription factor IRF2 binds TASOR2 (a) and colocalises to the same binding sites (b). IRF2 knockout suffices to abolish TASOR2 binding (c), implying that IRF2 recruits TASOR2 to ISGs. Depletion of TASOR2 derepresses IRF2-dependent transcription of ISGs (d).

5 Competition between HUSH and HUSH2 couples ISG induction to retroelement silencing

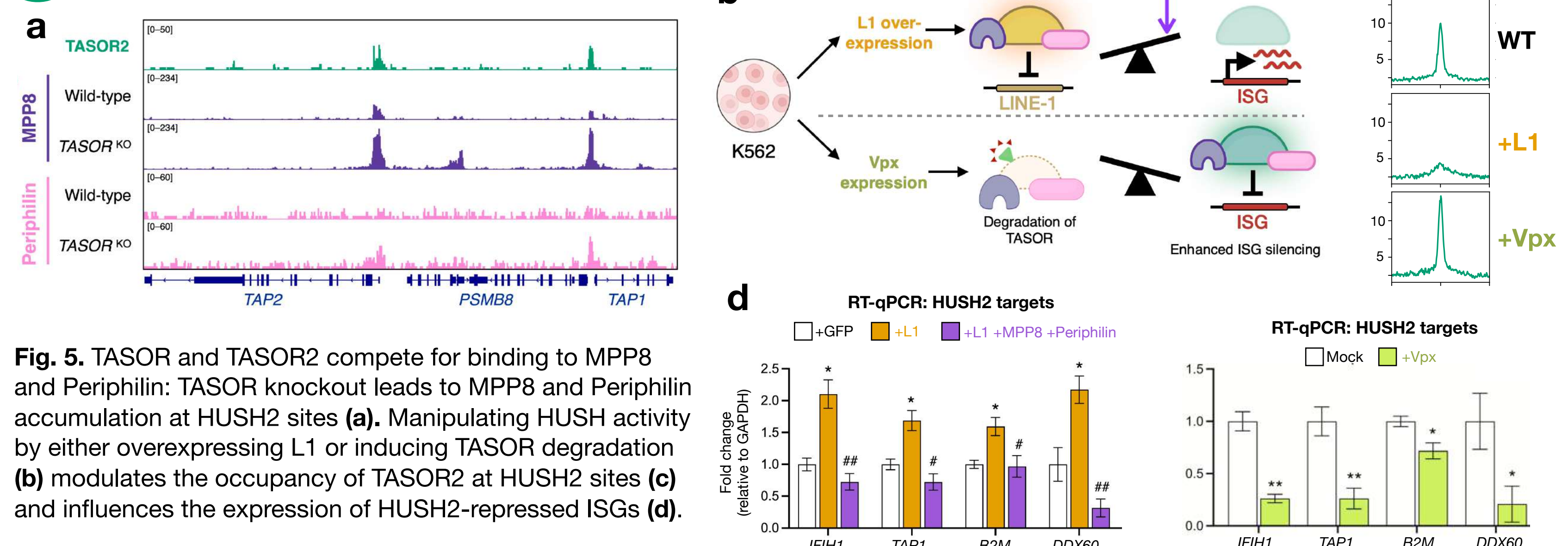


Fig. 5. TASOR and TASOR2 compete for binding to MPP8 and Periphilin: TASOR knockout leads to MPP8 and Periphilin accumulation at HUSH2 sites (a). Manipulating HUSH activity by either overexpressing L1 or inducing TASOR degradation (b) modulates the occupancy of TASOR2 at HUSH2 sites (c) and influences the expression of HUSH2-repressed ISGs (d).