Nucleosome–Chd1 structure and implications for chromatin remodelling

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Chromatin-remodelling factors change nucleosome positioning and facilitate DNA transcription, replication, and repair4. The conserved remodelling factor chromdomain-helicase-DNA binding protein 1 (Chd1)5 can shift nucleosomes and induce regular nucleosome spacing6,7. Chd1 is required for the passage of RNA polymerase II through nucleosomes8,9 and for cellular pluripotency7. Chd1 contains the DNA-binding domains SANT and SLIDE, a bilobal motor domain that hydrolyses ATP, and a regulatory double chromodomain. Here we report the cryo-electron microscopy structure of Chd1 from the yeast Saccharomyces cerevisiae bound to a nucleosome at a resolution of 4.8 Å. Chd1 detaches two turns of DNA from the histone octamer and binds between the two DNA gyres in a state poised for catalysis. The SANT and SLIDE domains contact detached DNA around superhelical location (SHL) −7 of the first DNA gyre. The ATPase motor binds the second DNA gyre at SHL +2 and is anchored to the N-terminal tail of histone H4, as seen in a recent nucleosome–Snf2 ATPase structure8. Comparisons with published results9 reveal that the double chromodomain swings towards nucleosomal DNA at SHL +1, resulting in ATPase closure. The ATPase can then promote translocation of DNA towards the nucleosome dyad, thereby loosening the first DNA gyre and remodelling the nucleosome. Translocation may involve ratcheting of the two lobes of the ATPase, which is trapped in a pre- or post-translocation state in the absence8 or presence, respectively, of transition state-mimicking compounds.

To investigate how RNA polymerase II transcribes through chromatin, we prepared factors that facilitate chromatin transcription in the yeast S. cerevisiae (Methods). These included the chromatin-remodelling enzyme Chd1, the histone chaperone FACT (facilitates chromatin transcription) and the transcription elongation factor Paf1C (polymerase-associated factor 1 complex). We formed a complex of these factors in the presence of the transition state-mimicking adduct ADP·BeF3 and a nucleosome with DNA comprising the Widom 601 sequence10 and 63 base pairs (bp) of extranucleosomal DNA (Methods, Extended Data Fig. 1a).

Cryo-electron microscopy (cryo-EM) analysis revealed nucleosome–Chd1 particles that had lost FACT and Paf1C (Methods, Extended Data Fig. 1b–d). The resulting reconstruction of the nucleosome–Chd1 complex at an overall resolution of 4.8 Å revealed protein secondary structures (Extended Data Fig. 2, Supplementary Video 1). Crystal structures of the nucleosome11,12 and Chd1 domains13–15 were unambiguously placed into the density. Only a minor, unassigned density remained that was located near histones H3 (residues 46–56) and H2A (residues 56–71) and may arise from a C-terminal domain14 in Chd1. A detailed structure was obtained after flexible fitting and real-space refinement (Extended Data Table 1).

The structure reveals an altered nucleosome with one engaged Chd1 molecule (Fig. 1). Two turns of nucleosomal DNA at SHL −5 to −7 are detached from the histone octamer. This alters the trajectory of extranucleosomal DNA by approximately 60° and breaks DNA interactions with histones H2A, H2B, and H3 (Fig. 2a). The ability of Chd1 to detach DNA depends on the presence of an ATP analogue or ADP·BeF3 (ref. 15), indicating that our structure trapped Chd1 in a state poised for activity. The histone octamer is unaltered compared to the free nucleosome, whereas it adopts an altered conformation in a nucleosome–ACF remodelling complex with ADP·BeF3 (ref. 16) (Extended Data Fig. 2g).

Chd1 binds between extranucleosomal DNA and the second DNA gyre at SHL +2 (Fig. 2, Extended Data Fig. 3), consistent with lower-resolution information17. Chd1 domains assemble between the two DNA gyres and form multiple DNA interactions. The SANT and SLIDE domains contribute to Chd1 affinity for the nucleosome22 and contact the first turn of extranucleosomal DNA in a way that has been previously observed for free DNA17. The ATPase engages with DNA at SHL +2, consistent with the structure of the related Snf2 ATPase bound to the nucleosome8 and with biochemical data9,23. The double chromodomain contacts DNA at SHL +1 (Extended Data Fig. 3b) and binds between the SANT domain and ATPase lobe 1. The structure is incompatible with binding of linker histone H118, explaining why H1 can repress Chd1-dependent remodelling8.

The ATPase motor adopts a closed conformation with the ADP·BeF3 adduct bound between lobes 1 and 2 (Fig. 3b). Compared to the free Chd1 structure22, lobe 2 rotates by approximately 40° towards lobe 1. This rotation closes the active site and positions the catalytic arginines ‘fingers’ in lobe 2 (R804 and R807), close to the ATP-binding site (Extended Data Fig. 3e). One of these arginine fingers is mutated in human CHD1 in prostate cancers21. These observations indicate that the structure captured Chd1 in a functional state poised for catalysis.

The ATPase motor interacts extensively with DNA (Fig. 2b, Extended Data Fig. 3a–c). On the basis of biochemical and structural observations9,25, we define the ‘tracking strand’ as the DNA strand running in the 5’ to 3’ direction from SHL +2 towards the histone octamer dyad. Lobe 1 contacts the tracking strand backbone with three protein regions, containing ATPase motifs Ia and Ic, and with a loop (residues 457–461) located between motifs Ia and Ib. The lobe 1 regions formed by motifs Ia and Ic contact the complementary ‘guide’ DNA strand. Lobe 2 interacts with the tracking strand via loops formed by motifs IV, IVa, and V. Residue W793 in motif Va inserts into the minor groove and contacts the guide strand backbone (Extended Data Fig. 3f). These ATPase–DNA interactions resemble the ‘primary’ interactions in a nucleosome–Snf2 complex8 and interactions observed in a distantly related ATPase–DNA complex23. The interactions support the model that Chd1 translocates along the DNA minor groove from SHL +2 away from the octamer dyad, thereby moving DNA towards the dyad24. Comparison of our structure with the nucleosome–Snf2 complex8 suggests a model for how ATP binding and hydrolysis result in DNA translocation (Supplementary Video 3). In the absence of ATP8, the ATPase is partially closed, whereas in the presence of ADP·BeF3 it is entirely closed (Extended Data Fig. 3e). Superposition of lobe 1 in these two structures results in different positions of lobe 2, which are
offset along the DNA by approximately one base pair in the direction of translocation (Fig. 2b). Provided that ATPases move in steps of one base pair, these observations suggest that the conformational ‘ratcheting’ between the ATPase lobes underlies DNA translocation.

According to this translocation model, the ATPase first binds DNA in a partially closed conformation (pre-translocation state). ATP binding then leads to complete closure of the ATPase and lobe 2 movement, which triggers DNA translocation by one base pair (post-translocation state). ATP hydrolysis then dissociates ADP and resets the ATPase to the pre-translocation state at the new DNA position. We speculate that directional translocation within this enzymatic cycle results from non-equivalent lobe 2 movements during translocation and ATPase resetting.

The structure also reveals the basis of ATPase activation by nucleosome binding (Fig. 3a). In the absence of the nucleosome, ATPase
Figure 3 | Chd1 structural changes and ATPase activation. a, Swinging of double chromodomain (open state, light pink; closed state, purple) onto DNA liberates ATPase lobe 2 (grey). The structure of free Chd1 in its inactive state was placed by superimposing ATPase lobe 1 (orange). In the inactive state, the chromo-wedge binds to a basic patch on lobe 2. View as in Fig. 1c. b, ATPase closure and activation. Lobe 2 (green) rotates by ~40° to allow binding of ADP·BeF$_3$ (grey spheres). BeF$_3$ was modelled in a tetrahedral conformation for simplicity but is likely to be planar when it mimics part of the pentavalent transition state of ATP hydrolysis.

lobe 2 is sequestered in an open conformation by the ‘chromo-wedge’, an acidic region in the double chromodomain. In the presence of the nucleosome, the double chromodomain swings by 15° and binds nucleosomal DNA. The chromo-wedge contacts the DNA backbone at SHL +1 (Extended Data Fig. 3b), using a region that contains sites that, when mutated in the human homologue CHD4, have been linked to cancer. Thus, binding of Chd1 to nucleosomal DNA induces swinging of the double chromodomain that releases lobe 2 and allows ATPase closure and activation (Supplementary Video 2). Chd1 recognizes bent nucleosomal DNA, as free DNA activates the ATPase only weakly and straight B-DNA would clash with the double chromodomain (Extended Data Fig. 3d).

Interactions of the double chromodomain with other Chd1 domains may compensate for the loss of histone–DNA contacts upon detach-
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**Supplementary Information** is available in the online version of the paper.

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Preparation of nucleosomal complexes. DNA fragments for nucleosome reconstruction were generated by PCR (Extended Data Fig. 3g), essentially as described previously\(^35\). A vector containing the Widom 601 sequence was used as a template for PCR. In-house expressed and purified Phusion polymerase was used for the PCR reaction with two primers (forward: CGCGTGTTCATGGATTTCCCTCTCTATGGGGCCTGATTAGAAGCTGCGAACTCGCGAGCACTGATCGATTTTATATCTGTCAGCTGCCCTGTC, reverse: ATGCAATCTCCGGTCGCG). The PCR program had the following steps: 1. 98 °C for 1 min, 2. 98 °C for 10s, 3. 72 °C for 1 min, 4. 98 °C for 1 min, 5. pause at 5 °C. PCR products were pooled from three-48 well PCR plates (100 μl per well). The products were ethanol-purified and resuspended in 1 μl TE buffer (10 mM Tris pH 8.0, 1 mM EDTA pH 8.0). The resuspended DNA was applied to a Resource Q 6 ml (GE Healthcare) and eluted with a gradient from 0–100% TE high salt buffer (10 mM Tris pH 8.0, 1 mM NaCl, 1 mM EDTA pH 8.0). Peak fractions were analysed on a 1% (v/v) TAE agarose gel and fractions containing the desired DNA product were pooled. The sample was ethanol-purified, resuspended in 200 μl TE buffer, and stored at –20 °C before use.

Nucleosome reconstitution was performed as described\(^37\), with minor modifications. Histone octamer and DNA were mixed at a 1:1 molar ratio in 2 M KCl, and transferred to Slide-A-Lyzer MINI Dialysis Units 20,000 MWCO (Thermo Scientific). The sample was gradient dialysed against low salt buffer (30 mM KCl, 20 mM Na·HEPES pH 7.5, 1 mM EDTA pH 8.0, 1 mM DTT) over 18 h. The sample was dialysed for another four hours against low salt buffer, recovered, and stored at 4 °C. Quantification of the reconstituted nucleosome was achieved by measuring absorbance at 280 nm. Molar extinction coefficients were determined for protein and nucleic acid components and were summed to yield a molar extinction coefficient for the reconstituted NCP.

To prepare a nucleosome–FACT complex, FACT, Chd1, and PeB were mixed at a molar ratio of 1:1:2:1.4, and incubated for 10 min. Zero monovalent salt buffer (2 mM MgCl\(_2\), 20 mM Na·HEPES pH 7.5, 5% (v/v) glycerol, 1 mM DTT) was added in the middle to attain a final monovalent salt concentration of 30 mM. Reconstituted NCP was added at a 0.5 molar ratio of the FACT concentration. The sample was incubated for 10 min, centrifuged (21,000g, 4 °C, 10 min), and applied to a Superose 6 Increase 3.2/300 column equilibrated in gel filtration buffer (30 mM NaCl, 2 mM MgCl\(_2\), 20 mM Na·HEPES pH 7.5, 5% (v/v) glycerol, 1 mM DTT). Peak fractions were pooled and ADP-BeF\(_2\) was added to a concentration of 1 mM ADP and 3 mM BeF\(_3\), and incubated for 10 min. The sample was cross-linked with 0.1% (v/v) glutaraldehyde and incubated for 10 min on ice. The cross-linking reaction was quenched for 10 min using a concentra-
tion of 90 mM Tris–HCl (pH 7.9), 9 mM lysisin and 9 mM aspartate. The sample was transferred to a Slide–A-Lyzer Mini Dialysis Unit 20,000 MWCO (Thermo Scientific), and dialysed for 6 h against 600 ml dialysis buffer (30 mM NaCl, 2 mM MgCl\(_2\), 20 mM Na·HEPES pH 7.4, 1 mM DTT). Cryo-EM and image processing. The nucleosome–Chd1–FACT–PeB1 complex sample was applied to R2/2 gold grids (Quantifoil). The grids were glow-discharged for 45 s before sample application of 2μl on each side of the grid. The sample was subsequently blotted for 8 s and vitrified by plunging into liquid ethane with a Vitrobot Mark IV (FEI Company) operated at 4°C at 100% humidity. Cryo-EM data were acquired on a FEI Titan Krios transmission electron microscope (TEM) operated at 300keV, equipped with a K2 summit direct detector (Gatan). Automated data acquisition was carried out using FEI EPU software at a nominal magnification of 105,000 x. Image stacks of 40 frames were collected in counting mode over 10 s. The dose rate was 3 e\(^{-}\) per Å\(^{2}\) per s for a total dose of 30 e\(^{-}\) Å\(^{2}\). A total of 3,806 image stacks were collected.

Frames were stacked and subsequently processed with MotionCor2\(^39\). CTFF correction was performed with Gcti\(^40\). Image processing was performed with RELION 2.1\(^41\) unless noted otherwise. Post-processing of refined models was performed using UCSF Chimera (RCSB PDB page). Cryo-EM reconstructions were performed using projections of an initial reconstruction (~400,000 particles, FEI Falcon 2, not shown), yielding 990,020 particle images. Particles were extracted with a box size of 224\(^2\) pixels, normalized, and screened using iterative rounds of reference-free 2D classification, yielding a total of 773,326 particles (Extended Data Fig. 1). Particle images were sub-divided into three batches and processed individually. Using a 40 Å low-pass filtered model from an initial reconstruction (not shown), we performed iterative rounds of hierarchical 3D classification with image alignment as outlined in Extended Data Fig. 1c. The three particle image batches were subsequently merged, re-extracted with a box size of 2,402 pixels, and subjected to 3D classification with image alignment. The best two classes were combined and subjected to a 3D refinement with a mask that encompasses the entire NCP–Chd1 complex. The NCP–Chd1 reconstruction was obtained from 67,032 particles with a resolution of 4.8 Å (gold-standard Fourier shell correlation 0.143 criterion). The map was sharpened with a B-factor of −20 Å\(^2\). Local resolution estimates were determined using a sliding window of 40 pixels, as previously
described. Resolutions for individual Chd1 domains were determined by masking the respective regions and performing B-factor sharpening (gold-standard Fourier shell correlation 0.143 criterion) using RELION.

**Model building.** Crystal structures of the *X. laevis* nucleosome with Widom 601 sequence (PDB code 3LZ0), the *S. cerevisiae* Chd1 DNA-binding domains (PDB code 3TED), and *S. cerevisiae* Chd1 core (double chromodomain and ATPase motor, PDB code 3MWY) were placed into the electron density using UCSF Chimera. The individual Chd1 domains (SANT, SLIDE, double chromodomain, ATPase lobe1, and ATPase lobe2) were fitted as rigid bodies. Residues 842–922 were removed from the double chromodomain–ATPase motor structure (PDB code 3MWY) owing to weak density. We did not observe assignable density for the CHCT domain of Chd1. We did not assign density near H3 (residues 46–56) and H2A (residues 56–71). Extranucleosomal DNA, nucleosomal DNA from SHL –7 to SHL –5, and the H4 N-terminal tail residues 16–20 were built using COOT. Three rounds of flexible fitting were performed with vmd and MDFF, resulting in good fits of the electron density. Secondary structure restraints were applied and the model was real-space refined against the post-processed EM map using PHENIX. ADP·BeF₃ was built by superpositioning ATP·gamma-S from the inactive Chd1 structure (PDB code 3MWY) onto our model, and replacing the ATP analogue with ADP·BeF₃ (PDB code 3ICE). ADP·BeF₃ was modelled in a tetrahedral conformation for simplicity but is likely to be planar when it mimics the ATP analogue with ADP·BeF₃. BeF₃⁻ was modelled as a part of the pentavalent transition state of ATP hydrolysis. While ADP is remarkably well-resolved at the given resolution, BeF₃⁻ has weaker density and was modelled on the basis of previous structural data from other ATPases. R804 and R807 were fitted manually. The complete structure was geometry-optimized with PHENIX. Figures were generated using PyMOL and UCSF Chimera. Electron density was shown for the local resolution filtered map, if not stated otherwise.

**Data availability.** The electron density reconstruction and final model were deposited with the Electron Microscopy Data Base (accession code 3765) and with the Protein Data Bank (PDB) (accession code 5O9G).

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Extended Data Figure 1 | Cryo-EM structure determination and analysis. a, Formation of the nucleosome–Chd1–FACT–Paf1C complex. SDS–PAGE of peak fraction used for cryo-EM grid preparation containing Chd1, FACT subunits, Paf1C subunits, and histones. The identity of the bands was confirmed by mass spectrometry. For gel source data, see Supplementary Fig. 1. b, Representative cryo-EM micrograph of data collection. c, 2D class averages contain nucleosome-like shapes. d, Sorting and classification tree used to reconstruct the nucleosome–Chd1 particle at 4.8 Å resolution. Steps 1 and 2 of batch 1 global classification are shown representatively for all three batches.
Extended Data Figure 2 | Quality of the nucleosome–Chd1 structure.
a, Overall fit of the nucleosome–Chd1 structure to the electron density. Two views are depicted as in Fig. 1b, c. b–f, Electron density (grey mesh) for various Chd1 domains reveals secondary structure and a good fit for DNA (SHL−4 to SHL+7).
g, Superposition of the histone octamer core with canonical octamer core (PDB code 3LZ0). The canonical octamer core is rendered in grey.
h, Nucleosome–Chd1 reconstruction coloured according to local resolution. Red dots indicate the presence of at least one particle image assigned within ±1°.

Shading from white to black indicates the density of particle images at a given orientation. j, Estimation of the average resolution. The dark blue line indicates the Fourier shell correlation (FSC) between the half maps of the reconstruction. The dotted light blue line indicates the Fourier shell correlation between the derived model and the reconstruction. Resolutions are given for the FSC 0.143 and the FSC 0.5 criteria. The dotted lines show the Fourier shell correlation between the derived Chd1 domains and the corresponding masked regions.

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Extended Data Figure 3 | Chd1–DNA interactions and Chd1 interaction interfaces. **a**, Overview of Chd1–DNA interactions. **b**, Contact of chromo-wedge with DNA at SHL +1. **c**, Secondary DNA contacts of ATPase. Contact of motif Ib with first DNA gyre around SHL –6. **d**, Modelling linear B-DNA (orange) onto the ATPase motor in the nucleosome–Chd1 structure leads to a clash with the double chromodomain (purple). B-DNA was superimposed onto nucleosomal DNA at SHL +2. **e**, ADP-BeF₃ binds in the active site of the Chd1 ATPase motor. Electron density is shown for ADP·BeF₃, motif I (Walker A, P-loop, residues 403–410), motif II (Walker B, residues 510–515), and the arginine fingers (R804 and R807). Motifs I and II are shown in ribbon representation. ADP-BeF₃ and the arginine finger residues are shown as sticks. The density for ADP is strong, whereas the density for BeF₃⁻ is weaker and thus we cannot formally rule out that BeF₃⁻ is not bound or shows only partial occupancy. **f**, Contact of W793 with the phosphate backbone of the guide strand at SHL +2. Electron density is shown as a grey mesh. **g**, Interface between the double chromodomain and the SANT and SLIDE domains of the DNA binding region. Chd1 domains are coloured as in Fig. 1a. **h**, Sequence of the Widom 601 sequence with 63 bp of extranucleosomal DNA.
Extended Data Figure 4 | ATPase conservation and histone H4 tail binding. a, Chd1 binds the N-terminal tail of histone H4 (green) with ATPase lobe 2 (surface representation coloured according to electrostatic surface potential; red, negative; white, neutral; blue, positive). The view is the inverse of that in Fig. 1b (that is, after a 180° rotation). b, Chd1 ATPase activity results in DNA translocation towards the octamer dyad, loosening DNA gyre 1 and triggering nucleosome remodelling. c, Sequence alignment of ATPase regions in S. cerevisiae (Sc) Chd1 (356–883), ScIsw1 (177–689), ScSnf2 (746–1270), Homo sapiens (Hs) Chd4 (703–1233), Drosophila melanogaster (Dm) Mi-2 (707–1231), and Sulfolobus solfataricus (Sso) Rad54 (423–802). Arginine ‘fingers’ of ScChd1 (R804 and R807) are indicated and ATPase motifs are underlined. Sequence coloured according to identity. Darker shades of blue indicate higher conservation, whereas lighter shades of blue indicate less conservation. Alignment was generated with MAFFT51 and visualized using JalView52.

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Extended Data Table 1 | Cryo-EM data collection, refinement, and validation statistics

|                         | Nucleosome-Chd1 structure (EMDB-3765) (PDB 5O9G) |
|-------------------------|-----------------------------------------------------|
| **Data collection and processing** |                                                     |
| Microscope              | FEI Titan Krios                                      |
| Detector                | Gatan K2 Summit                                      |
| Magnification           | 105,000X                                             |
| Voltage (kV)            | 300                                                  |
| Electron exposure (e⁻/Å²) | 30                                                  |
| Defocus range (μm)      | 1.25 to 2.75                                         |
| Pixel size (Å)          | 1.35                                                 |
| Symmetry imposed        | C1                                                   |
| Initial particle images (no.) | 990,020                              |
| Final particle images (no.) | 67,032                                  |
| Map resolution (Å)      | 4.8                                                  |
| FSC threshold           | 0.143                                                |
|                         |                                                     |
| **Refinement**          |                                                     |
| Initial models used (PDB code) | 3LZ0, 3MWY, 3TED                                    |
| Map sharpening B factor (Å²) | -204                                                 |
| Model composition       |                                                     |
| Non-hydrogen atoms      | 19667                                                |
| Protein residues        | 1934                                                 |
| Ligands                 | 2                                                    |
| Validation              |                                                     |
| MolProbity score        | 1.93                                                 |
| Clashscore              | 7                                                    |
| Poor rotamers (%)       | 0.36                                                 |
| Ramachandran plot       |                                                     |
| Favored (%)             | 90.81                                                |
| Allowed (%)             | 9.06                                                 |
| Disallowed (%)          | 0.13                                                 |
## Experimental design

1. **Sample size**
   - Describe how sample size was determined.
   - N/A

2. **Data exclusions**
   - Describe any data exclusions.
   - N/A

3. **Replication**
   - Describe whether the experimental findings were reliably reproduced.
   - All attempts at replication were successful.

4. **Randomization**
   - Describe how samples/organisms/participants were allocated into experimental groups.
   - N/A

5. **Blinding**
   - Describe whether the investigators were blinded to group allocation during data collection and/or analysis.
   - N/A

Note: all studies involving animals and/or human research participants must disclose 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).

```
- 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 (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- The test results (e.g. P values) given as exact values whenever possible and with confidence intervals 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
```

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.

RELION 2.0.4, MotionCor2, PHENIX, MDFF, vmd, coot

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 for-profit company.

No unique materials were used.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

N/A

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

SF9 cell line (Thermo Scientific, Waltham, MA, USA), SF21, HIS insect cell lines (Expression Systems, Davis, CA, USA)

b. Describe the method of cell line authentication used.

N/A

c. Report whether the cell lines were tested for mycoplasma contamination.

N/A

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.

N/A

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

N/A

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.

N/A