Cryo-electron microscopy structure of a nucleosome-bound SWI/SNF chromatin remodeling complex

Yan Han[1], Alexis A Reyes[1,2], Sara Malik[1], Yuan He[1,2,3,4,*]

1. Department of Molecular Biosciences, Northwestern University, Evanston, IL, USA

2. Interdisciplinary Biological Sciences Program, Northwestern University, Evanston, USA

3. Chemistry of Life Processes Institute, Northwestern University, Evanston, IL, USA

4. Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Northwestern University, Chicago, USA

*Corresponding author (yuanhe@northwestern.edu)

Abstract

The multi-subunit chromatin remodeling complex SWI/SNF[1-3] is highly conserved from yeast to humans and plays critical roles in various cellular processes including transcription and DNA damage repair[4,5]. It uses the energy from ATP hydrolysis to remodel chromatin structure by sliding and evicting the histone octamer[6-10], creating DNA regions that become accessible to other essential protein complexes. However, our mechanistic understanding of the chromatin remodeling activity is largely hindered by the lack of a high-resolution structure of any complex from this family. Here we report the first structure of SWI/SNF from the yeast *S. cerevisiae* bound to a nucleosome at near atomic resolution determined by cryo-electron microscopy (cryo-EM). In the structure, the Arp module is sandwiched between the ATPase and the Body module of the complex, with the Snf2 HSA domain connecting all modules. The HSA domain also extends into the Body and anchors at the opposite side of the complex. The Body contains an assembly scaffold composed of conserved subunits Snf12 (SMARCD/BAF60), Snf5 (SMARCB1/BAF47/ INI1) and an asymmetric dimer of Swi3 (SMARCC/BAF155/170). Another conserved subunit Swi1 (ARID1/BAF250) folds into an Armadillo (ARM) repeat domain that resides in the core of the SWI/SNF Body, acting as a molecular hub. In addition to the interaction between Snf2 and the nucleosome, we also observed interactions between the conserved Snf5 subunit and the histones at the acidic patch, which could serve as an anchor point during active DNA translocation. Our structure allows us to map and rationalize a subset of cancer-related mutations in the human SWI/SNF complex and propose a model of how SWI/SNF recognizes and

remodels the +1 nucleosome to generate nucleosome-depleted regions during gene activation[11-13].

Main

To gain insight into the molecular mechanisms of how SWI/SNF remodels chromatin, we purified endogenous SWI/SNF from *S. cerevisiae*, assembled the SWI/SNF-nucleosome complex *in vitro* (Extended Data Fig. 1) and determined its structure using single particle cryo-EM. The complex was assembled in the presence of the non-hydrolysable ATP analog ADP-BeF_x and was determined to sub-nanometer resolution (Extended Data Fig. 2). We observed that the nucleosome is clamped between two regions of the SWI/SNF complex (Fig. 1, Supplementary Video 1). To improve the resolution, we also assembled the complex in the presence of ATPγS and determined its structure using cryo-EM (Extended Data Fig. 3). Since this structure shows features similar to the ADP-BeF_x bound complex, we combined the two data sets and performed further processing (Extended Data Fig. 4). After careful 3D classification, we obtained a reconstruction of the body of SWI/SNF to an average resolution of 4.7 Å (Fig. 1a; Extended Data Fig. 4), which we refer to as the Body module of SWI/SNF. This resolution allowed the *de novo* model building of the SWI/SNF complex (Fig. 1b).

In addition to the bound nucleosome, the SWI/SNF complex is composed of three major modules: the Body, the Arp, and the ATPase (Fig. 2a). The Snf2 ATPase domain binds the nucleosome at super helical location (SHL) 2, the same location shown in the stand-alone structures of the Snf2 ATPase-nucleosome complexes[14,15] as well as in SWR1[16], Chd1[17,18] and SNF2h[19], but quite different from INO80[20,21] (Extended Data Fig. 5). The Arp module is composed of Arp7, Arp9, Rtt102 and the HSA domain of Snf2 and is sandwiched between the Body and the ATPase modules (Fig.1a, b). This architecture

has never been observed before and is quite different from other multi-subunit remodeling complexes, including INO80 and SWR1[16,20,21] (Extended Data Fig. 5). The HSA of Snf2 plays an essential role in connecting the ATPase and Arp modules to the Body, extending into the Body and anchoring at the opposite side of the complex (Fig. 1a, b). We therefore named this region of Snf2 adjacent to the HSA the Anchor domain (Fig. 1c). This connection of the Arp module to the Body through a single α helix could explain the observed flexibility of the Arp and ATPase modules in the reconstruction as evidenced by lower estimated local resolution (Extended Data Figs. 2, 3). The functional relevance of this flexibility requires further investigation.

The 4.7 Å resolution map of the Body shows the helical nature of the SWI/SNF (Fig. 1a) and enabled us to build a structural model with the help of prior knowledge of this important complex (Figs. 1b, 2; Methods). We then mapped the crosslinking data for apo SWI/SNF[22] onto our model of the Body module as a validation procedure (Extended Data Table 1). Out of the 35 inter-linking pairs that were mapped onto the Body model, 27 (77%) pairs have a Cα-Cα distance within 30 Å, the maximum distance that is allowed by using the crosslinker BS3[23]. We also mapped 60 pairs of intra-links, of which 55 (92%) show a Cα-Cα distance within 30 Å. These comparisons demonstrate the accuracy of our model, and also indicates that the structure of the SWI/SNF Body module does not change drastically upon engaging a nucleosome.

The conserved subunits Swi1/ARID1/BAF250, Swi3/SMARCC/BAF150/177, Snf12/ SMARCD/BAF60 and Snf5/ SMARCB1/BAF47/INI1 assemble into the body of the

SWI/SNF complex (Fig. 2), consistent with these proteins forming a core module in the human SWI/SNF complexes[24]. Based on the positioning of different domains and their functions, we further defined four sub-modules of the scaffold — the Spine, the Hinge, the Arm and the Core (Fig. 2a).

The Spine is composed of Snf12 and the C-terminal regions of Swi3 (Fig. 2b). We identified two copies (named A and B) of Swi3 in our structure, consistent with previous crosslinking data showing multiple same-residue crosslinks within Swi3[22]. The most striking feature of the Spine is the four-helix bundle formed by the two long helices (LH1/2) of Snf12 and the Coiled-coil domains from two Swi3 (Fig. 2b), consistent with previous finding that the RSC homologs of Snf12 (RSC6) and Swi3 (RSC8) directly interact[25]. The Coiled-coil domain of Swi3 has clear leucine-zipper properties, containing hydrophobic amino acids separated by 7 residues in a helical region[26]. Interestingly, the crystal structure of the human dominant-negative OmoMYC homodimer[27], a leucine-zipper containing complex, can be unambiguously fitted into the two helices belonging to Swi3 by rigid body docking (Extended Data Fig. 6a). Surprisingly, the two Coiled-coil domains of Swi3 have different lengths (Fig. 2b), showing an asymmetric folding (Extended Data Fig. 6b). We speculate that this might be due to the different interactions that the two Coiled-coils are involved in during complex assembly. BAF155/170 (SMARCC1/2), the human homologues of Swi3, have been indicated to form a dimer at the very first step of SWI/SNF complex assembly[24]. We therefore hypothesize that the two copies of Swi3 are indistinguishable at the early steps of SWI/SNF assembly, and that after engaging with other subunits, especially

Snf12/SMARCD/BAF60, the symmetry is broken. Snf12 has been shown to play important roles in SWI/SNF function[28], and our structure suggests that it may do so by interacting with Swi3 and contributing to the assembly of the complex. The unassigned density at the tip of the Spine shows clear β-sheet features and is directly connected to the SWIB domain of Snf12 (Extended Data Fig. 6c). This, together with the secondary structure prediction of Snf12, allowed us to assign this density to Snf12.

The Hinge is composed of the two SANT domains of Swi3 and the C-terminal helices of Snf12 (Fig. 2c). SANT^{B} contacts the C-terminal helices of Snf12 and is in close proximity to the Core sub-module (Fig. 2c), whereas SANT^{A} is located at the top and interacts with a C-terminal segment of Swi3^{A} (Fig. 2c). Both SANT domains contact and sandwich the Snf2 Anchor domain (Fig. 2c), playing a key role in stabilizing the ATPase within the complex.

The Arm is composed of Snf5, the N-terminal SWIRM domains of Swi3 and C-terminus of Swp82 (Fig. 2d). The Snf5 Core repeat (RPT) domains each engage one copy of the Swi3 SWIRM domain in a similar manner as in the human BAF47/BAF155 crystal structure[29] (Fig. 2d, Extended Data Fig. 7a, b). Subtle differences in the two RPT-SWIRM interfaces (Extended Data Fig. 7c) are likely due to the α helix N-terminal to RPT1, H-N, wedging between RPT1 and SWIRM^{A} while the C-terminal region of RPT2 is packed against the opposite side of SWIRM^{B}. The RPT1/SWIRM^{A} connects the Arm module to the Core module by tightly associating with Swi1 (Fig. 2d). Swp82 contains an α helix that runs along Snf5/Swi3 (Fig. 2d), likely further stabilizing the Arm module.

The environments that the two molecules of Swi3 experience in both the Hinge and the Arm further establish the asymmetric architecture of this homodimer (Extended Data Fig. 6b).

Swi1/ARID1/BAF250 resides in the core region of the Body, acting as a hub to integrate all other modules (Fig. 2a, e). Therefore, we name it the Core module. It clearly folds into an Armadillo (ARM) repeat structure[30] (Fig. 2e, Extended Data Fig. 8a). Interestingly, BAF250a, the human homolog of Swi1, was predicted to contain an ARM domain[31], consistent with the highly conserved nature of this subunit. Compared to the β-catenin structure[32], the Swi1 ARM repeat domain contains extra insertion sequences (Extended Data Fig. 8a), such as the one between helices H3 and H6. In addition to the neighboring repeats, this long insertion makes extensive contacts with the Snf5 and Swi3 subunits of the Arm as well as both the Spine and the Hinge. It contacts the Arm by wrapping on top of the Swi3 $SWIRM^A$ domain and traveling back along the Snf5 H-N (Extended Data Fig. 8b). Interestingly, this insertion also forms an α helix H4 that contacts a surface on $SWIRM^B$, whose corresponding region on $SWIRM^A$ engages with Swi1 H1 and Snf5 H-N (Extended Data Fig. 7d), emphasizing the role of Swi1 in associating with the Arm module. In addition to this long insertion associating with the Arm, H1 of Swi1 contacts the $SWIRM^A$ domain of Swi3, whereas H3 and H8 interact with Snf5 RPT1 (Extended Data Fig. 8b), thus connecting the Arm to the Core. The Swi1 ARM repeat domain also interacts extensively with the Spine sub-module. The entire top surface of the Swi1 ARM makes contacts with the helix bundle from the

Spine, with the C-terminal helices H19 and H20 engaging the SWIB domain of Snf12 (Extended Data Fig. 8c).

The Core is also the major docking point of the Snf2 Anchor domain (Fig. 3a). H11 of Swi1 ARM interacts with an extended region of the Snf2 HSA domain that is absent from the crystal structure[33], while H2, H6 and H9 contact the Anchor linker (Extended Data Fig. 9a). These interactions, together with the Hinge region sandwiching the Anchor helices of Snf2 (Extended Data Fig. 9b), further lock the ATPase in the complex. This observation is consistent with ARID1A being the branching subunit connecting the ATPase module with the rest of the SWI/SNF complex in humans[24].

The modular architecture of the SWI/SNF complex revealed by our structure agrees well with the modules revealed by previous biochemical and proteomic studies[34,35]. The conserved SWI/SNF subunits form the structural scaffold within the complex, whereas yeast-specific subunits only occupy peripheral regions. For example, Snf6 was identified to situate at the back of the complex, spanning the Core and wrapping on top of the four-helix bundle of the Spine (Extended Data Fig. 10a). Swp82 is another yeast-specific subunit, and it is also located peripherally, making limited contacts with the rest of the complex (Extended Data Fig. 10b). Based on our sequence conservation analysis (Supplementary Figures 1-5), we have also mapped a subset of invariant residues from the human cancer mutation database[36] onto our SWI/SNF model. Although the majority of the mutations likely compromise structure and folding, many also map to protein-protein interfaces, contributing to different types of the human disease (Fig. 2b-e, 3a).

Our structure has also enabled us to map the interactions between the SWI/SNF complex and the nucleosome. The ATPase domain of Snf2 binds the nucleosome at SHL2 in the context of the entire complex, as reported previously for the stand-alone ATPase[14,15,37,38]. A series of cancer patient mutations map to the Snf2 HSA-DNA interface near SHL-6, likely diminishing the remodeling efficiency by disrupting protein-DNA interactions (Fig. 3a). The yeast-specific subunit Swp82 also contacts the nucleosomal DNA near SHL-2 (Fig. 3b), likely contributing to the remodeling activity of SWI/SNF. Although the nucleosomal DNA is not deformed as was observed for Chd1[17,18], there are multiple interactions between the SWI/SNF complex and the extranucleosomal DNA in our structure. First, Snf6 contacts the extranucleosomal DNA proximal to the nucleosome (Fig. 3b), in good agreement with previous site-directed DNA crosslinking experiments[39]. Second, at a lower threshold, we observed additional density for extranucleosomal DNA contacting the Body module (Extended Data Fig. 11), suggesting flexibility of this region of the DNA. However, when we prepared the SWI/SNF-nucleosome complex using a nucleosome with no overhanging DNA sequence (data not shown), we failed to observe stable complex formation, suggesting the importance of the extranucleosomal DNA in nucleosome binding to SWI/SNF. Interestingly, this extranucleosomal DNA also coincides with the possible trajectories of the N-terminal regions of both Swi1 and Snf5 (Extended Data Fig. 11), which have been shown to interact with acidic transcription activators[40-42]. This could explain how SWI/SNF is recruited by transcription activators to its target loci for chromatin remodeling, leading to an activated gene transcription.

A connecting density is observed between the histones and Snf5 C-terminus (Fig. 3c, d), consistent with the histone crosslinking experiments[22,39]. This density likely corresponds to the highly conserved Snf5 arginine anchor motif that interacts with the acidic patch of the histone octamer (Fig. 3c, d) where a number of nucleosome regulators bind[43], suggesting a conserved mechanism of octamer recognition. Deletion of the RPT domains in Snf5 uncouples ATP hydrolysis by Snf2 with the chromatin remodeling activity[22]. Our structure suggests an anchoring role of the Arm sub-module during active remodeling, in which Snf5 locks the histones in place as the nucleosomal DNA is being translocated, thus coupling ATP hydrolysis with chromatin remodeling (Fig. 4). In contrast, this anchoring role is primarily carried out by the Arp module in other large remodeling complexes, including INO80 and SWR1[16,20,21] (Extended Data Fig. 5). It has been well documented that the natural substrate for SWI/SNF is the +1 nucleosome situated near the promoter[11-13]. Therefore, the extranucleosomal DNA at the exit side of the nucleosome in our structure corresponds to upstream promoter DNA, consistent with SWI/SNF's function in generating the nucleosome-depleted regions during gene activation.

Methods

SWI/SNF purification.

SWI/SNF complex was purified from a yeast strain containing a TAP tag at the C-terminus of Snf2[44] (obtained from the High Throughput Analysis Laboratory at Northwestern University). Tandem affinity purification was performed as following. The tagged yeast strain was grown to an optical density at 600nm (OD_{600}) of 4-5 in 12 liters of YPD (3% glucose). Next, cells were harvested by centrifugation and washed with 200 ml of cold TAP Extraction Buffer (40 mM Tris pH 8, 250 mM ammonium sulfate, 1mM EDTA, 10% glycerol, 0.1% Tween 20, 5 mM dithiothreitol [DTT], 2 mM phenylmethylsulfonyl fluoride [PMSF], 0.31 mg/ml benzamidine, 0.3 µg/ml leupeptin, 1.4 µg/ml pepstatin, 2 µg/ml chymostatin). Cells were resuspended in 150 ml cold TAP Extraction Buffer and lysed in a BeadBeater (Biospec Products). Cell debris was removed by centrifugation at 14,000 ×g at 4°C for 1 hr. For the first affinity step, 2 ml IgG Sepharose beads (GE Healthcare) were incubated with the lysate at 4°C overnight. The beads were next washed and resuspended in 4 ml cold TEV (tobacco etch virus) Cleavage Buffer (10 mM Tris pH8, 150 mM NaCl, 0.1% NP-40, 0.5 mM EDTA, 10% glycerol). TEV cleavage using 25 µg of TEV protease was performed at room temperature for 1 hr with gentle shaking. The TEV protease-cleaved products were collected, and the IgG beads were washed with 3 column volumes (~6 ml total) cold Calmodulin Binding Buffer (15 mM HEPES pH7.6, 1 mM magnesium acetate, 1 mM imidazole, 2 mM $CaCl_2$, 0.1% NP-40, 10% glycerol, 200 mM ammonium sulfate, 5 mM DTT, 2 mM PMSF, 0.31 mg/ml benzamidine, 0.3 µg/ml leupeptin, 1.4 µg/ml pepstatin, 2 µg/ml chymostatin). $CaCl_2$ was added to the combined eluate at a final concentration of

2 mM and incubated with 0.8 ml Calmodulin Affinity Resin (Agilent Technologies) at 4°C for 2 hours. After incubation, the beads were washed with cold Calmodulin Binding Buffer and cold Calmodulin Wash Buffer (same as Calmodulin Binding Buffer, but containing 0.01% NP-40), and bound proteins were eluted with Calmodulin Elution Buffer (15 mM HEPES pH 7.6, 1 mM magnesium acetate, 1 mM imidazole, 2 mM EGTA, 10% glycerol, 0.01% NP-40, 200 mM ammonium sulfate) at room temperature. Fractions containing the SWI/SNF complex were combined and concentrated to a final concentration of ~4 mg/ml (280 nm absorption) using a concentrator (Amicon Ultra-4 Ultracel 30K, Millipore). Concentrated protein was aliquoted, flash frozen in liquid nitrogen and stored at -80℃.

Nucleosome reconstitution.

Mono-nucleosome was reconstituted with Xenopus histones and the 601 DNA[45] using the Mini Prep Cell (Bio-rad) as described previously[46]. The Xenopus histones were obtained from the Histone Source – the Protein Expression and Purification (PEP) Facility at Colorado State University. DNA oligonucleotides containing the 601 sequence were purchased from IDT (Integrated DNA Technology): top strand, 5'-ACCTCCCACTATTTTATGCGCCGGTATTGAACCACGCTTATGCCCAGCATCGTTAATCGATGTATATATCTGACACGTGCCTGGAGACTAGGGAGTAATCCCCTTGGCGGTTAAAACGCGGGGGACAGCGCGTACGTGCGTTTAAGCGGTGCTAGAGCTGTCTACGACCAATTGAGCGGCCTCGGCACCGGGATTCTGAT-3'; bottom strand, 5'-ATCAGAATCCCGGTGCCGAGGCCGCTCAATTGGTCGTAGACAGCTCTAGCACCGCTTAAACGCACGTACGCGCTGTCCCCCGCGTTTTAACCGCCAAGGGGATTACTCCC

TAGTCTCCAGGCACGTGTCAGATATATACATCGATTAACGATGCTGGGCATAAGCG TGGTTCAATACCGGCGCAT-3'. The 601 sequence is underlined. The lyophilized DNA oligos were resuspended in water to a final concentration of ~100 μM and mixed at 1:1 molar ratio. Annealing of the DNA was performed by incubating in boiling water for 5 min followed by gradually cooling to room temperature in 2 hours. The reconstituted nucleosome core particle (NCP) was concentrated to ~6μM and annealed with a biotinylated RNA molecule (IDT, 5'-UAGUGGGAGGU-3'-biotin) to the top DNA strand at 1:1.5 (DNA to RNA) molar ratio at 45℃ for 5 min followed by gradually cooling to room temperature in 30-40 min. This resulted in a final concentration of the nucleosome core particle (NCP) at 5.52 μM. The annealed NCP was stored at 4℃.

SWI/SNF-NCP assembly.

To assemble the SWI/SNF-NCP complex, we modified our approach of reconstituting Pol I/II/III pre-initiation complexes (PIC)[47-49] and used the NCP to replace the nucleic acid scaffold. Specifically, 0.4 μl of the biotin-RNA-annealed NCP (0.552 μM, 1/10 of the storage concentration) was first mixed with 1μl of the assembly buffer (12 mM HEPES pH 7.9, 0.12 mM EDTA, 12% glycerol, 8.25 mM $MgCl_2$, 1 mM DTT, 2 mM ADP, 32mM KF, 4mM $BeCl_2$ and 0.05% NP-40 [Roche]). Next, 1 μl of the concentrated SWI/SNF complex was added to this mixture and incubated at room temperature for 2 hours. Assembled complex was immobilized onto the magnetic streptavidin T1 beads (Invitrogen) which had been equilibrated with the assembly buffer plus 60 mM KCl and minus ADP-BeF_x. Following washing of the beads two times using a wash buffer (10 mM HEPES, 10 mM Tris, pH 7.9, 5% glycerol, 5 mM $MgCl_2$, 50 mM KCl, 1 mM DTT,

0.05% NP-40, 1 mM ADP, 16mM KF, 2mM $BeCl_2$), the complex was eluted by incubating the beads at room temperature for 30 min with 3µl digestion buffer containing 10 mM HEPES, pH 7.9, 10 mM $MgCl_2$, 50 mM KCl, 1 mM DTT, 5% glycerol, 0.05% NP-40, 1 mM ADP, 16mM KF, 2mM $BeCl_2$ and 0.05 unit/µl RNase H (New England Biolabs). The SWI/SNF-NCP complex assembled in the presence of ATPγS was performed essentially as described above with 1mM (2mM in the first assembly buffer) ATPγS replacing ADP-BeF_x in the buffers.

Electron microscopy.

The assembled SWI/SNF-NCP complex was first crosslinked using 0.05% glutaraldehyde under very low illumination conditions on ice for 5 min before applied onto EM grids. Negative staining sample preparation and data collection were performed as previously described[48]. For cryo sample preparation, crosslinked complex (~3.3 µl) was applied onto a 400 mesh Quantifoil grid containing 3.5 µm holes and 1 µm spacing (Quantifoil 3.5/1, Electron Microscopy Sciences). A thin carbon film was floated onto the grid before it was plasma cleaned for 10s at 5 W power using a Solarus plasma cleaner (Gatan) equipped with air immediately before sample deposition. The sample was allowed to absorb to the grid for 10 min at 4℃ and 100% humidity in a Vitrobot (FEI) under low illumination conditions, before blotted for 4 s at 10 force and plunge-frozen in liquid ethane. The frozen grids were stored in liquid nitrogen until imaging.

Cryo-EM data collection was performed using a JEOL 3200FS transmission electron microscope (JEOL) equipped with a K2 Summit direct electron detector (Gatan)

306 operating at 200kV (Extended Data Table 2). Data were collected using the K2 camera
307 in counting mode at a nominal magnification of 30,000 × (1.12 Å per pixel). Movie series
308 with defocus values ranging from -1.5 to -4.5 µm were collected using Leginon[50]. 40-
309 frame exposures were taken at 0.3 s per frame (12 s total), using a dose rate of 8 e^- per
310 pixel per second, corresponding to a total dose of 76.5 e^- $Å^{-2}$ per movie series. Four
311 datasets with a total number of 7,769 movies on the ADP-BeF_x sample and four other
312 datasets with a total number of 6,903 movies on the ATPγS sample were collected.
313
314 **Image processing and three-dimensional reconstruction.**
315 Negative stain data pre-processing was performed using the Appion processing
316 environment[51]. Particles were automatically selected from the micrographs using a
317 difference of Gaussians (DoG) particle picker[52]. The contract transfer function (CTF) of
318 each micrograph was estimated using CTFFind4[53], the phases were flipped using
319 CTFFind4, and particle stacks were extracted using a box size of 128 × 128 pixels.
320 Two-dimensional classification was conducted using iterative multivariate statistical
321 analysis and multi-reference alignment analysis (MSA-MRA) within the IMAGIC
322 software[54]. Three-dimensional (3D) reconstruction of negative stained data was
323 performed using an iterative multi-reference projection-matching approach containing
324 libraries from the EMAN2 software package[55]. The initial 3D model was generated using
325 cryoSPARC[56].
326
327 Cryo-EM data was pre-processed as follows. Movie frames were aligned using
328 MotionCor2[57] to correct for specimen motion. Particles were automatically selected from

the aligned and dose-weighted micrographs using Gautomatch (developed by Zhang K, MRC Laboratory of Molecular Biology, Cambridge, UK) with 2-fold binnning (corresponding to 2.24Å/pixel). The CTF of each micrograph and of each particle was estimated using Gctf[58]. All three-dimensional (3D) classification and refinement steps together with postprocess and local resolution estimation were performed within RELION 3.0[59].

For the ADP-BeF_x dataset, 891,573 particles were automatically picked and were subjected to an initial round of 3D classification with alignment using the density obtained from negative staining as the initial reference (Extended Data Fig. 2). The "Angular sampling interval", "Offset search range (pix)" and "Offset search step (pix)" were set to 15 degrees, 10 and 2, respectively, for the first 50 iterations. Next, these values were set back to default (7.5 degrees, 5, 1) and the 3D classification was continued until convergence. This resulted in class 3 with 198,543 particles showing sharp structural features of SWI/SNF and nucleosome. This class was subsequently refined and further classified without alignment into 5 classes with a mask around the Arp module and the nucleosome (Extended Data Fig. 2b). Class 1 with 35,214 particles from this second round of classification showed best features of the nucleosome and was chosen to proceed with 3D auto-refinement, which yielded a structure of SWI/SNF-NCP at an overall resolution of 8.96Å (Extended Data Fig. 2c). All resolutions reported herein correspond to the gold-standard Fourier shell correlation (FSC) using the 0.143 criterion[60]. The ATPγS dataset with 820,117 particles was processed in a similar manner (Extended Data Fig. 3), resulting in a structure with an overall resolution of 10Å.

352

353 To focus on the Body of SWI/SNF, we combined the particles from both samples after
354 the first round of 3D classification with a total number of 390,573 particles (Extended
355 Data Fig. 4). Next, signal subtraction on the nucleosome and the lower half of the Arp
356 module was performed as previously described[61], leaving the SWI/SNF Body module
357 and the top half of the Arp module intact. Subsequently, a 3D classification was
358 performed with only local alignment turned on. This resulted in class 5 with 61,518
359 particles showing the best structural features of the Body module (Extended Data Fig.
360 4b). Next, we unbinned and refined the original particle stack of this class, and
361 generated masks around the Body module, the Arp module plus the ATPase density of
362 Snf2, and the nucleosome (Extended Data Fig. 4b). 3D multi-body refinement[62] was
363 then performed on this class, which drastically improved the resolution of the Body
364 module to 4.7Å (Extended Data Fig. 4c). The core region of the Body module has a
365 resolution close to 4.3Å (Extended Data Fig. 4b), showing densities of bulky sidechains,
366 which enabled us to partially build the structural model of the Body module (Fig. 1b).
367 This body map replaced its corresponding region in the ADP-BeF_x map to result in the
368 composite map shown in Fig. 1a.

369

370 **Model building.**

371 To aid in model building, we performed secondary structure prediction of the SWI/SNF
372 subunits using the Genesilico Metaserver[63]. Sequence alignment of the conserved
373 SWI/SNF subunits were performed using CLC Sequence Viewer 7 (Supplementary
374 Figures 1-5). To build the structural model of the SWI/SNF Body module, we first

375 performed rigid body docking of known structures into our 4.7Å Body map. The rigid-
376 body docking was performed in UCSF Chimera[64,65], which yielded good fit of the
377 following structures: the SNF5 Repeat domains (RPTs) and Swi3 SWIRM domains from
378 the human BAF47/BAF155 complex (PDB ID 5GJK)[29], the SANT domain of the yeast
379 Swi3 (PDB ID 2YUS), and the SWIB domain of mouse BAF60a (PDB ID 1UHR). The
380 BAF47/BAF155 heterodimer and the Swi3 SANT domain can be docked in the density
381 map at two distinct locations, indicating two copies of these domains. Indeed, chemical
382 crosslinking combined with mass spectrometry has shown at least two copies of Swi3 in
383 the yeast SWI/SNF complex[22], confirming our docking experiment. Yeast Snf5 has been
384 annotated with two SNF5 RPT domains in Pfam (http://pfam.xfam.org/protein/P18480).
385 We observed clear density in our map that connects these two RPT domains. Next, we
386 built homology models of these structures using Modeller[66] and replaced the docked
387 PDBs in the Body density map. Regions with missing or extra connecting density were
388 then manually deleted or built in Coot[67] based also on secondary structure predictions
389 of these proteins.
390
391 The Snf2 Anchor domain was built manually in Coot. First, the Arp7/Arp9/Rtt102/HSA
392 structure (PDB ID 4I6M)[33] was rigid body docked into the full map, which helped in
393 registering the HSA helix in the Body map. The HSA helix was then manually extended
394 in Coot, with Y586 matching a sidechain density further confirming the register of this
395 helix. Next, the Anchor domain was manually extended from the end of the HSA by
396 following the connected density of the map. Again, secondary structure prediction was

also used as a guide when extending the model in Coot. Bulky sidechain density at Y497, Y533 and W554 further confirmed the model.

The ARM repeat domain of Swi1 locates in the core region of the Body map with the highest local resolution, therefore enabling *de novo* model building. First, the helix density corresponding to residues 942-955 of Swi1 was chosen to model because it has the highest local resolution and that it contains a few bulky sidechain densities. Next, two α helices with poly-alanine sequence were generated in Coot, which allowed us to create a bulky residue (lysine, arginine, histidine, methionine, phenylalanine, tyrosine, and tryptophan) pattern along both directions. Subsequently, these patterns were used to search against the sequences of SWI/SNF subunits on the Sequence pattern search server (http://www-archbac.u-psud.fr/genomics/patternSearch.html), and Swi1 942-955 was one of the best hit. Further extension of this helix into connected density also matched the secondary structures of Swi1. Then, the remaining regions of the Swi1 ARM repeat domain were manually built into the density in Coot based on secondary structure prediction as well as bulky sidechain densities wherever possible. The overall architecture of the ARM repeat domain of Swi1 also matches that of an Armadillo repeat containing protein β-catenin[32] (Extended Data Fig. 8a), confirming our model of Swi1.

The positioning of the SWIB domain of Snf12 aided us in building the remaining of this protein into the density. First, at the Spine tip, where the SWIB was docked, there is β-sheet like density (Extended Data Fig. 6c). This agrees with the secondary structure prediction of Snf12, which shows β-strands right N-terminus of the SWIB domain.

Although the resolution of this region is low, we are confident about its identity. Four long helices belonging to the Spine module directly connect to this region, two of which extending into the Snf12 densities. Therefore, we assigned these two helices to Snf12. This agreed well with the secondary structure prediction of Snf12, which shows that Snf12 contains two long helices. Next, we performed protein sequence pattern search based on the bulky sidechain densities. Based on the search results, we manually built the two helices of Snf12 in Coot.

Based on secondary structure prediction, we reasoned that the other two long helices belong to Swi3 C-terminus. This is backed up by the finding that the C-terminus of Swi3 contains a coiled-coil leucine zipper motif[26] and there are two copies of Swi3 in SWI/SNF. To facilitate the registering of the sequence in these long helices, we fitted the crystal structure of human OmoMYC homodimer (PDB ID 5I4Z)[27] into the density and obtained a good fit (Extended Data Fig. 6a). Based on this fitting, we mapped the hydrophobic residues from Swi3 as indicated before[26] and manually built the two helices in Coot. The rest of Swi3 density cannot be confidently modeled due to lower resolution and missing density, therefore are modeled with poly-alanine.

Snf6 was also manually built in Coot based on secondary structure prediction, bulky sidechain density and prior knowledge based on chemical crosslinking and mass spectrometry data[22] and site-directed DNA crosslinking experiments[39]. We cannot confidently model in Swp82, however we were able to assign densities to this yeast specific subunit based on crosslinking experiments[22] and mapping by deletions and

EM[68]. The N-terminal region of Swp82 forms a RSC7 homology domain, therefore we speculate that it occupies the globular density near the Hinge; C-terminal region crosslinks to both Snf5 and Swi3, therefore it was assigned to the density by Snf5 and Swi3. There are also several unassigned densities on the solvent exposed surface of the complex. We did not identify Taf14 and Snf11 in the map (Extended Data Table 3).

The molecular model of SWI/SNF Body module was then refined using Namdinator[69] (Extended Data Table 2). To obtain the model for the full complex, we rigid-body fitted the Body, the Arp module (PDB ID 4I6M)[33] and the ATPase-nucleosome bound with ADP-BeF_x (PDB ID 5Z3V)[15] into the map of the full complexes in Coot. Then, the HSA helix was connected manually, and the DNA sequence was modified to match our sequence. The extra DNA was manually extended by 10bp using B form DNA in Coot. The figures were prepared using UCSF Chimera and ChimeraX[70]. Cα-Cα distances from crosslinked lysine pairs[22] were measured in UCSF Chimera. For crosslinks involving the two molecules of Swi3, we picked the combination that gave the shortest distance as the measurement (Extended Data Table 1).

Data availability

Cryo-EM density maps have been deposited in the Electron Microscopy Data Bank (EMDB) under accession numbers EMD-XXXX (ADP-BeF_x), EMD-XXXX (ATPγS), EMD-XXXX (body). Model coordinates have been deposited in the Protein Data Bank (PDB) under accession numbers XXXX (ADP-BeF_x), XXXX (body).

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Author contributions

Y Han and Y He conceived the project. Y Han performed most of the experiments and collected and analyzed cryo-EM data with Y He. AA Reyes and S Malik contributed to protein purification. Y Han built the models with help from Y He. Y Han and Y He wrote the manuscript, with input from all other authors.

Main Figures

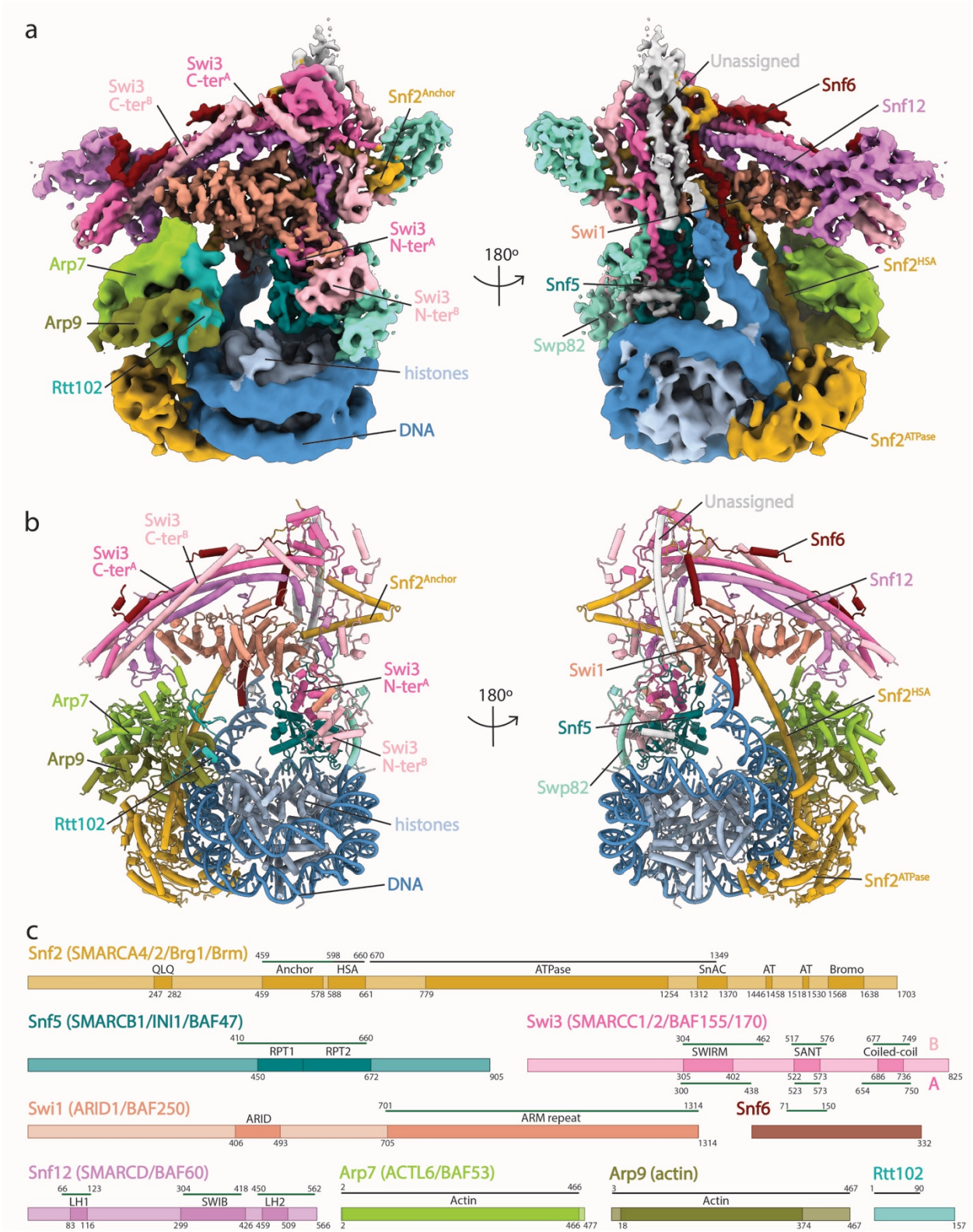

Fig. 1: Cryo-EM structure of the SWI/SNF-nucleosome complex. a, Front (left) and back (right) views of the cryo-EM composite map (see Methods) of the SWI/SNF-nucleosome complex assembled in the presence of ADP-BeF_x. **b**, Same views of structural model of the SWI/SNF-nucleosome complex as in **a**. **c**, Domain organization of all subunits that has been built in the model from **b**. Mammalian homologs are shown in parentheses. Newly built or homology regions are highlighted by green lines with residue numbers, whereas previous structures that were rigid body docked in our map are indicated by black lines. Subunits in **b** and **c** are colored as in **a**. Abbreviations: QLQ, Glutamine-Leucine-Glutamine; HSA, Helicase/SANT-associated; SnAC, Snf2 ATP coupling; AT, AT hook DNA-binding motif; RPT, Snf5 core repeat; SWIRM, a protein domain found in SWI3, RSC8 and MOIRA; SANT, SWI3, ADA2, N-CoR and TFIIIB" DNA-binding; ARID, AT-rich interaction domain; ARM repeat, Armadillo repeat; LH1/2, long helix 1/2; SWIB, SWI complex BAF60b.

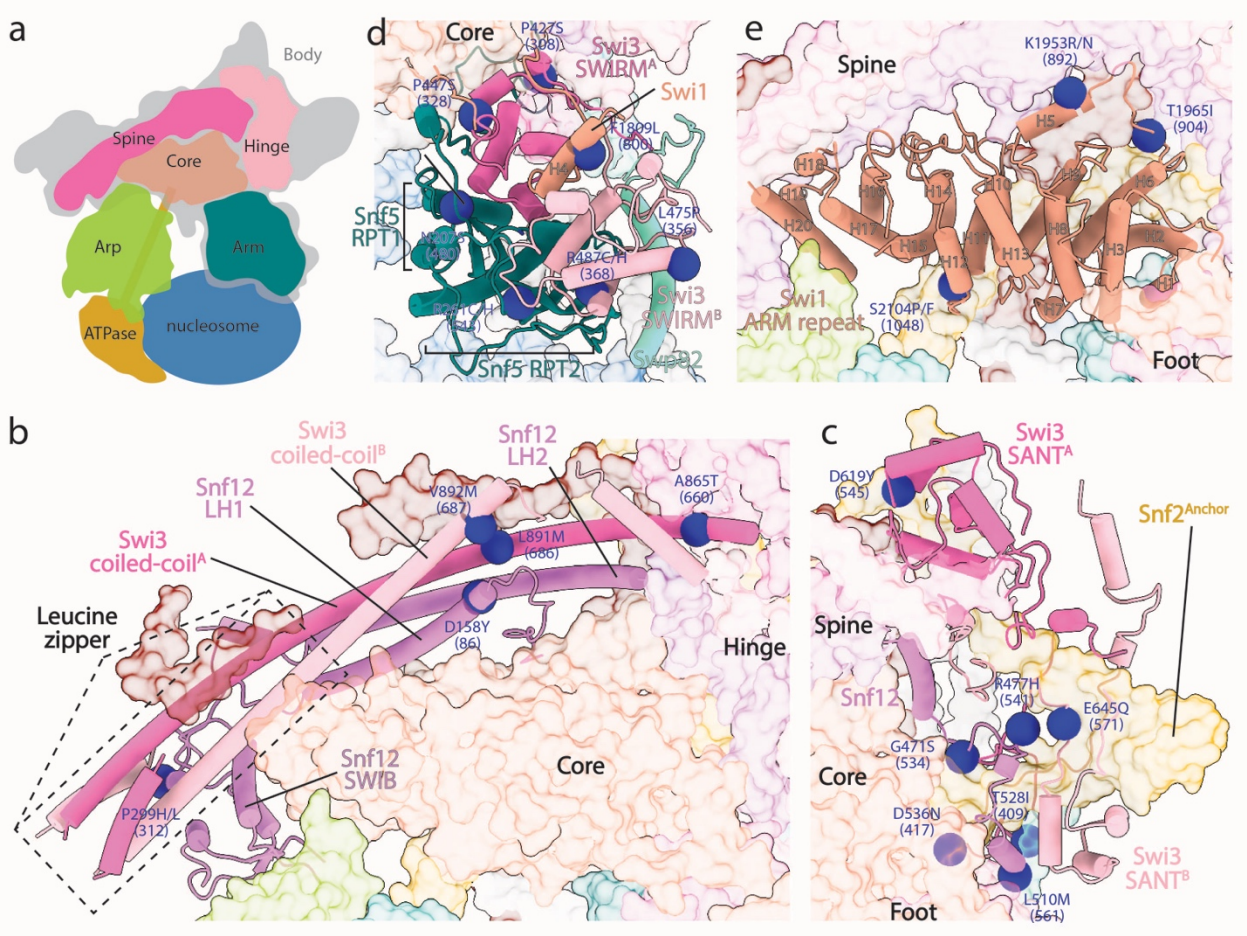

Fig. 2: Structural organization of the Body module of SWI/SNF. a, A cartoon depicting the molecular architecture of the SWI/SNF-nucleosome complex. **b-e**, Close-up view of detailed interactions within the Spine (**b**), the Hinge (**c**), the Arm (**d**) and the Core (**e**) sub-modules, respectively. Blue spheres depict the locations of a subset of invariant residues harboring cancer patient mutations that occur at interfaces between these conserved subunits. Subunits are colored the same as in **Fig. 1**.

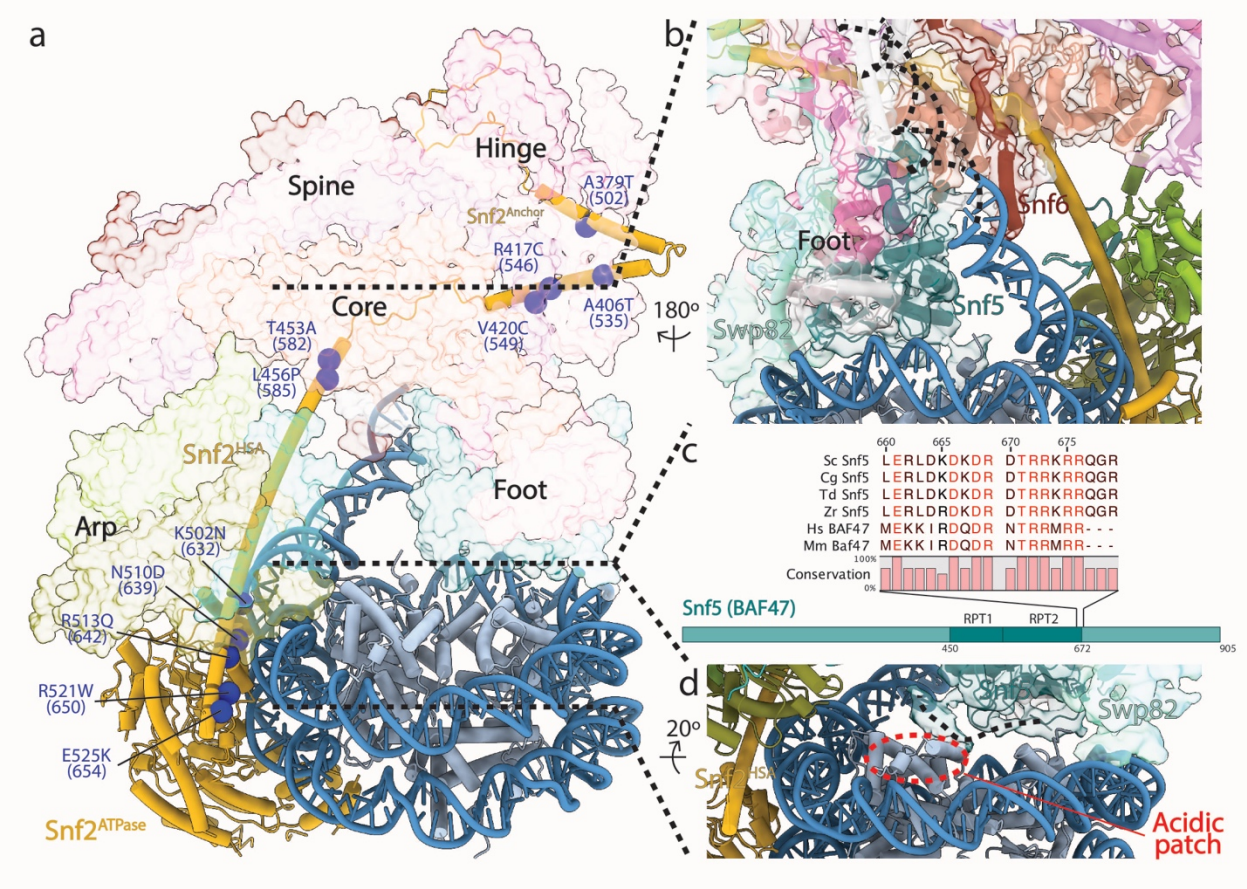

Fig. 3: SWI/SNF-nucleosome interactions. a, An overview of the SWI/SNF-nucleosome complex depicting how the HSA and Anchor domains of Snf2 load the ATPase onto the nucleosome. Blue spheres indicate the positions of a subset of invariant residues harboring cancer patient mutations in Snf2/SMARCA4/BRG1 that reside between conserved SWI/SNF subunits. Dotted lines indicate regions enlarged in **b** and **d**. **b**, Close-up view showing the interaction between SWI/SNF subunits and the nucleosomal DNA. **c**, Sequence alignment of the C-terminal extension of Snf5 RPT2. Sc, *Saccharomyces cerevisiae*; Cg, *Candida glabrata*; Td, *Torulaspora delbrueckii*; Zr, *Zygosaccharomyces rouxii*; Hs, *Homo sapiens*; Mm, *Mus musculus*. Domain organization of Snf5/SMARCB1/INI1/BAF47 is also shown as in **Fig. 1c**. **d**, Close-up

526 view showing the C-terminal extension (dotted line) of Snf5 RPT2 contacting the acidic

527 patch of the nucleosome (dotted red circle).

528

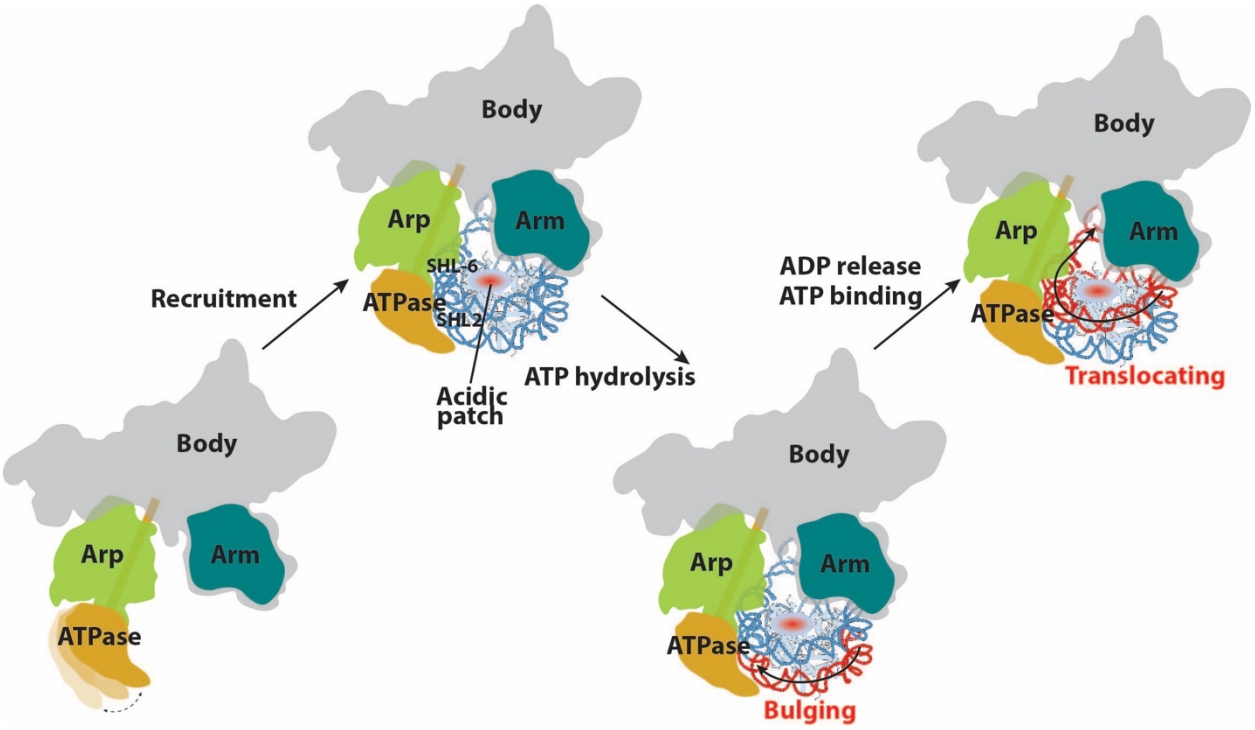

Fig. 4: Model for chromatin remodeling activity by the SWI/SNF complex. Prior to engagement with nucleosome, the ATPase module of SWI/SNF is flexible[68]. Nucleosome binding involves the ATPase and the HSA of Snf2 recognizing SHL2 and SHL-6, respectively. The Arm of SWI/SNF interact with the nucleosome surface near the acidic patch, likely serving as an anchor during active remodeling to keep the octamer from moving. Upon ATP hydrolysis, a bulge in the nucleosomal DNA is introduced at SHL 2[15], which is then propagated to the Exit side of the nucleosome when ADP is released and the next ATP molecule is bound, resulting in nucleosomal DNA translocation.

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