Literature review: DNA remodelers

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Three general remodeling processes

- assembly (spacing nucleosomes)
- access (exposing promoters)
- editing (incorporating histone H3.3)

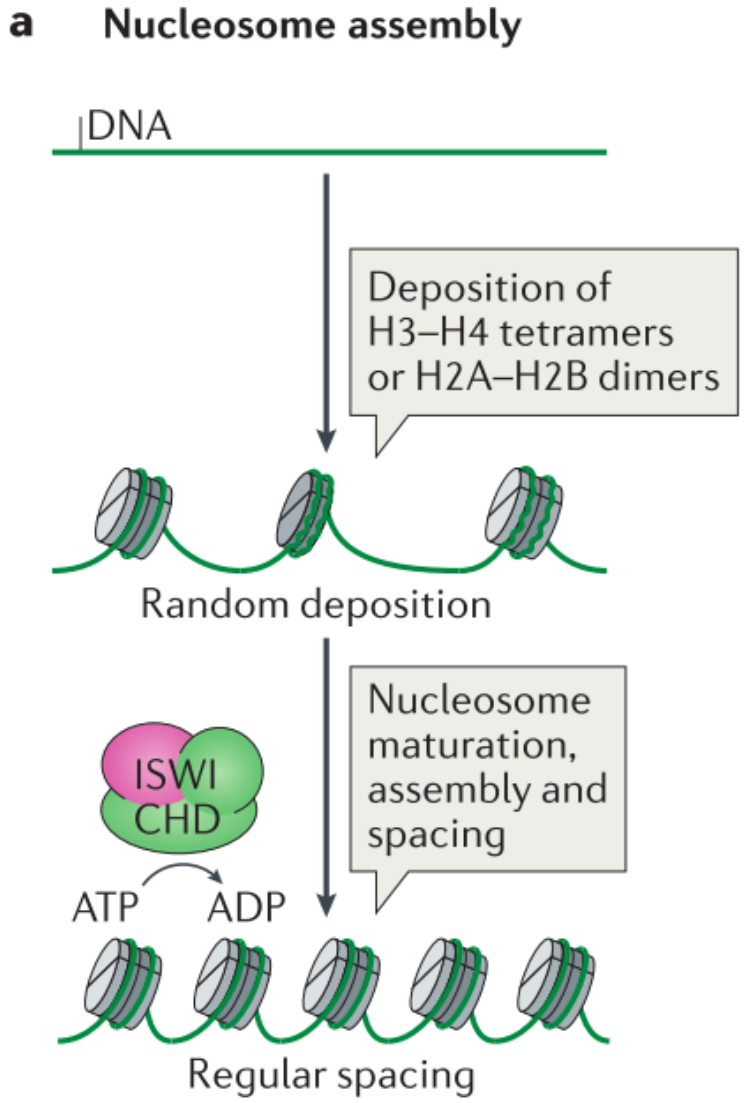
Remodeler classification

- ISWI subfamily (imitation swtich)
- SWI/SNF subfamily (switch/ sucrose non-fermentable)
- INO80 subfamily (inositol regulatory gene 80)
- CHD subfamily (chromodomain helicase DNA-binding)
- Sometimes SNR1

- Classification is on the basis of the similarities and differences in their catalytic ATPases and associated subunits.

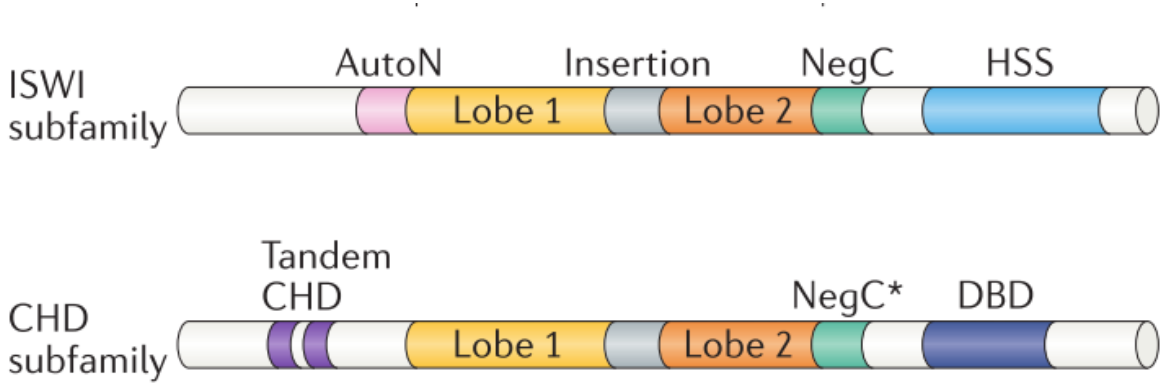
ISWI subfamily

- Central role in chromatin assembly after DNA replication and maintenance of higher-order chromatin structures.
- Organize nucleosome into proper bundle form and create equal spacing between nucleosomes
- Assemble and regularly space nucleosomes to limit chromatin accessibility and gene expression.
- The protein ISWI can interact with several proteins giving three different chromatin-remodeling complexes in Drosophila melanogaster: ***NURF***(nucleosome remodeling factor), ***CHRAC*** (chromatin remodeling and assembly complex) and ***ACF*** (ATP-utilising chromatin remodeling and assembly Factor).



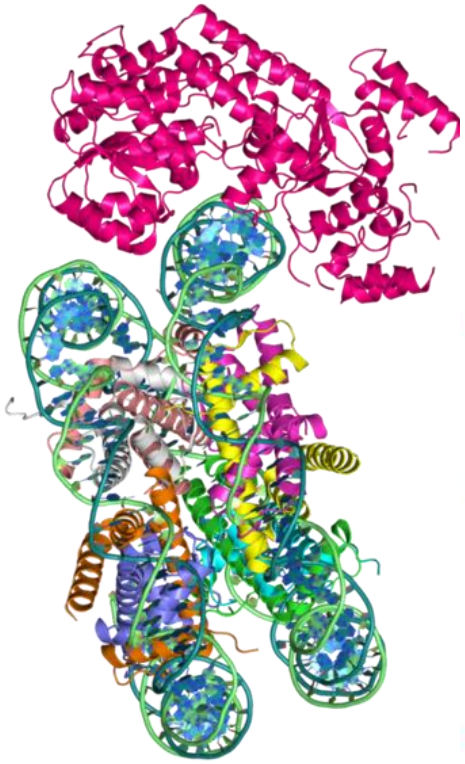
CHD subfamily

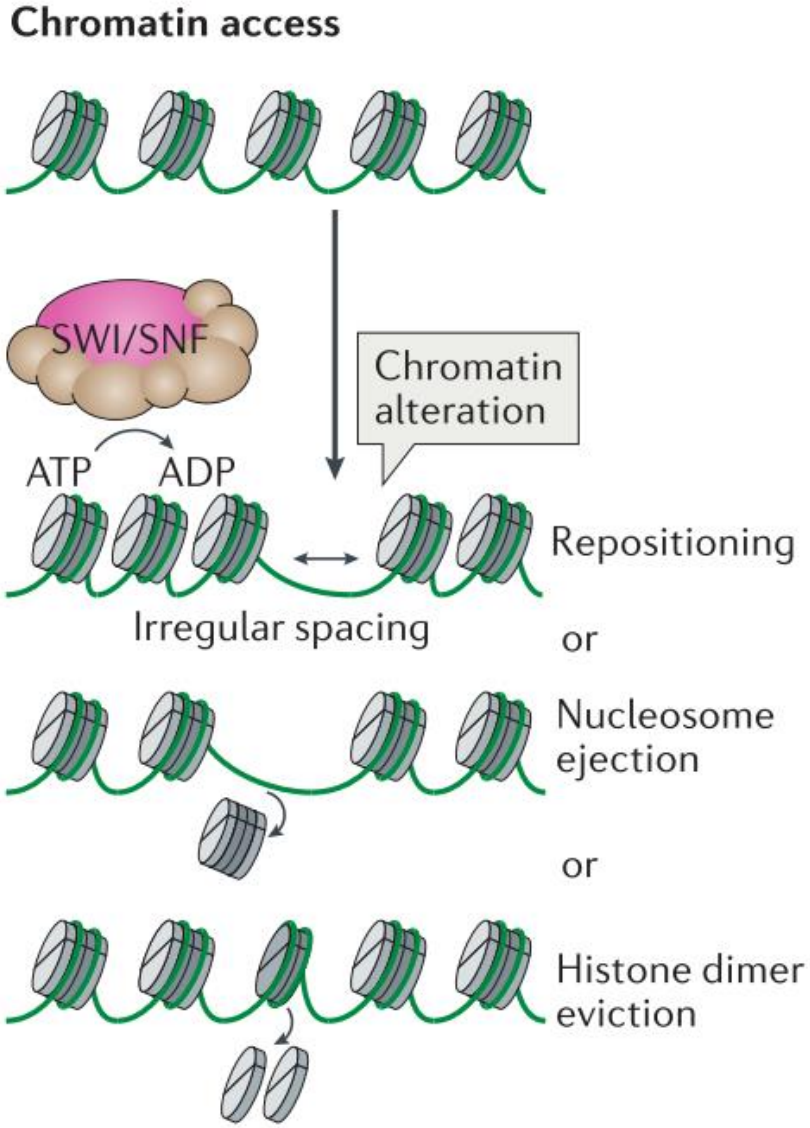
- CHD remodeling complexes primarily mediate transcriptional repression in the nucleus and are required for the maintenance of pluripotency of embryonic stem cells
- Different functional complexes (Chd1 – monomeric, NuRD – complex)
- Chd1 mainly conducts chromatin assembly, whereas the metazoan nucleosome remodelling deacetylase (NuRD) helps repressors to bind to chromatin and represses genes through its associated histone deacetylases



SWI/SNF subfamily

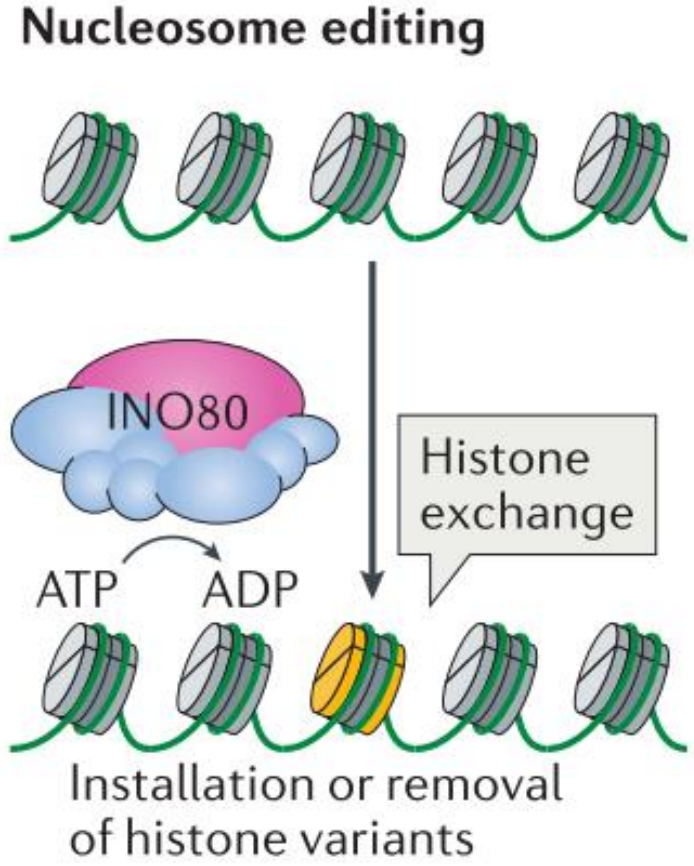
- Repositioning nucleosomes, ejecting octamers or evicting histone dimers. Used for either gene activation or gene repression.
- “Loop-recapture" mechanism involves the dissociation of DNA at the edge of the nucleosome with reassociation of DNA inside the nucleosome, forming a DNA bulge on the octamer surface. The DNA loop would then propagate across the surface of the histone octamer in a wave-like manner, resulting in the repositioning of DNA without changes in the total number of histone-DNA contacts



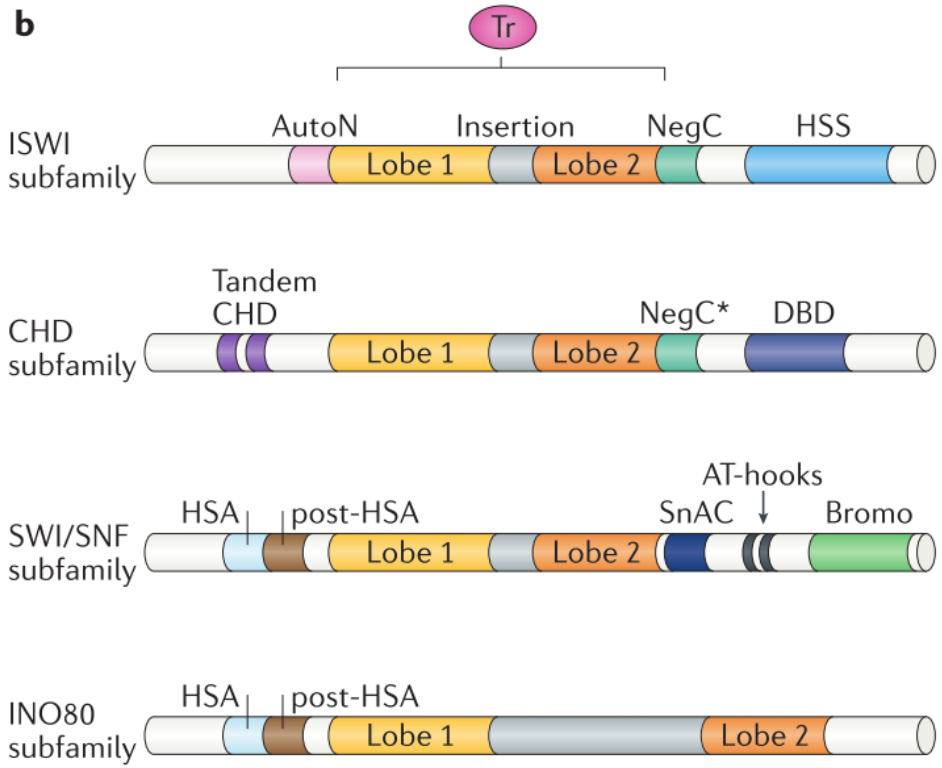


INO80 subfamily + SWR1

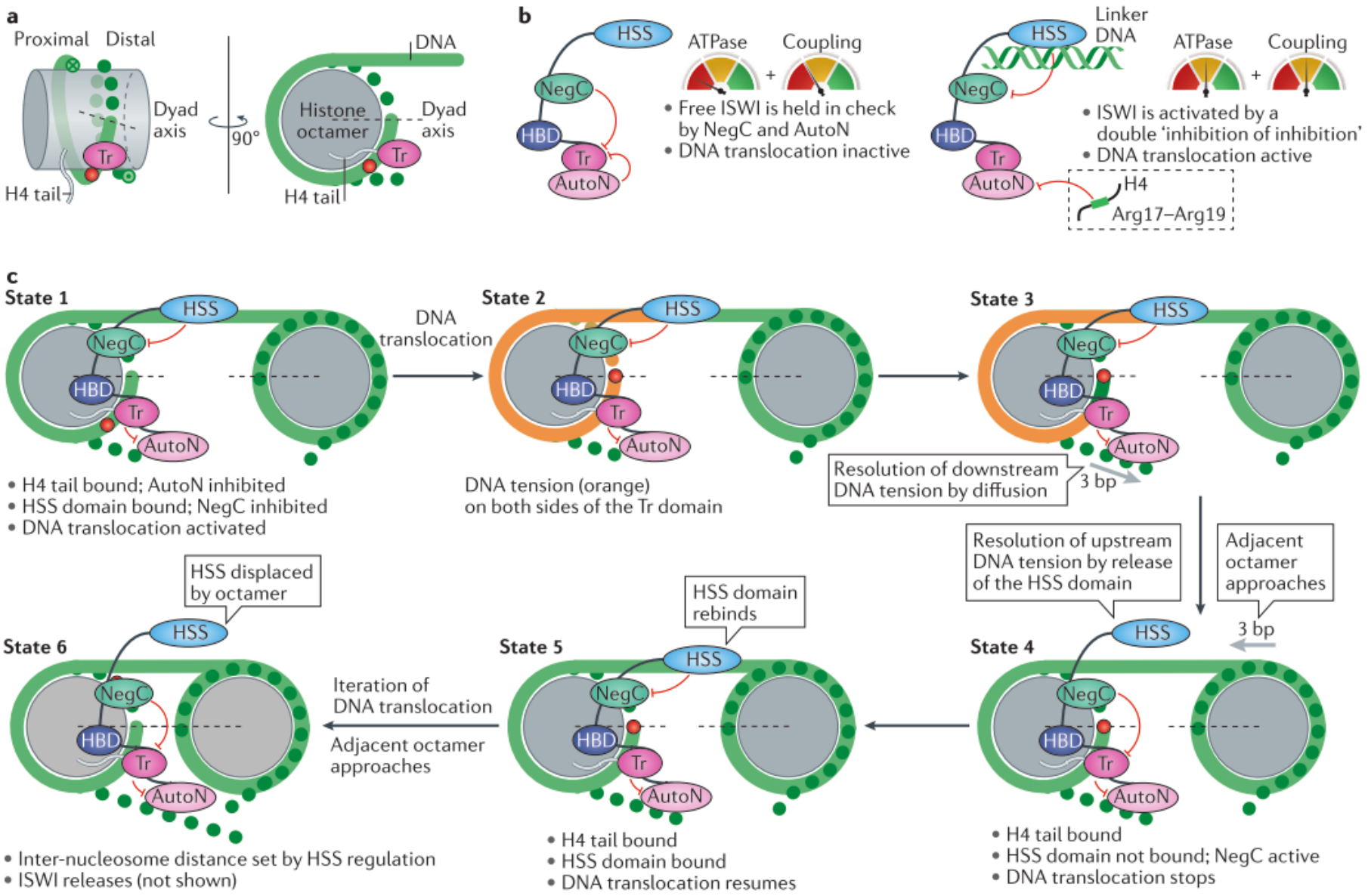
- Change nucleosome composition by exchanging canonical and variant histones, for example, and installing H2A.Z variants
- Participate in DNA double-strand break (DSB) repair and nucleotide-excision repair (NER) and thereby plays crucial role in TP53 mediated DNA-damage response (same as SWI/SNF)



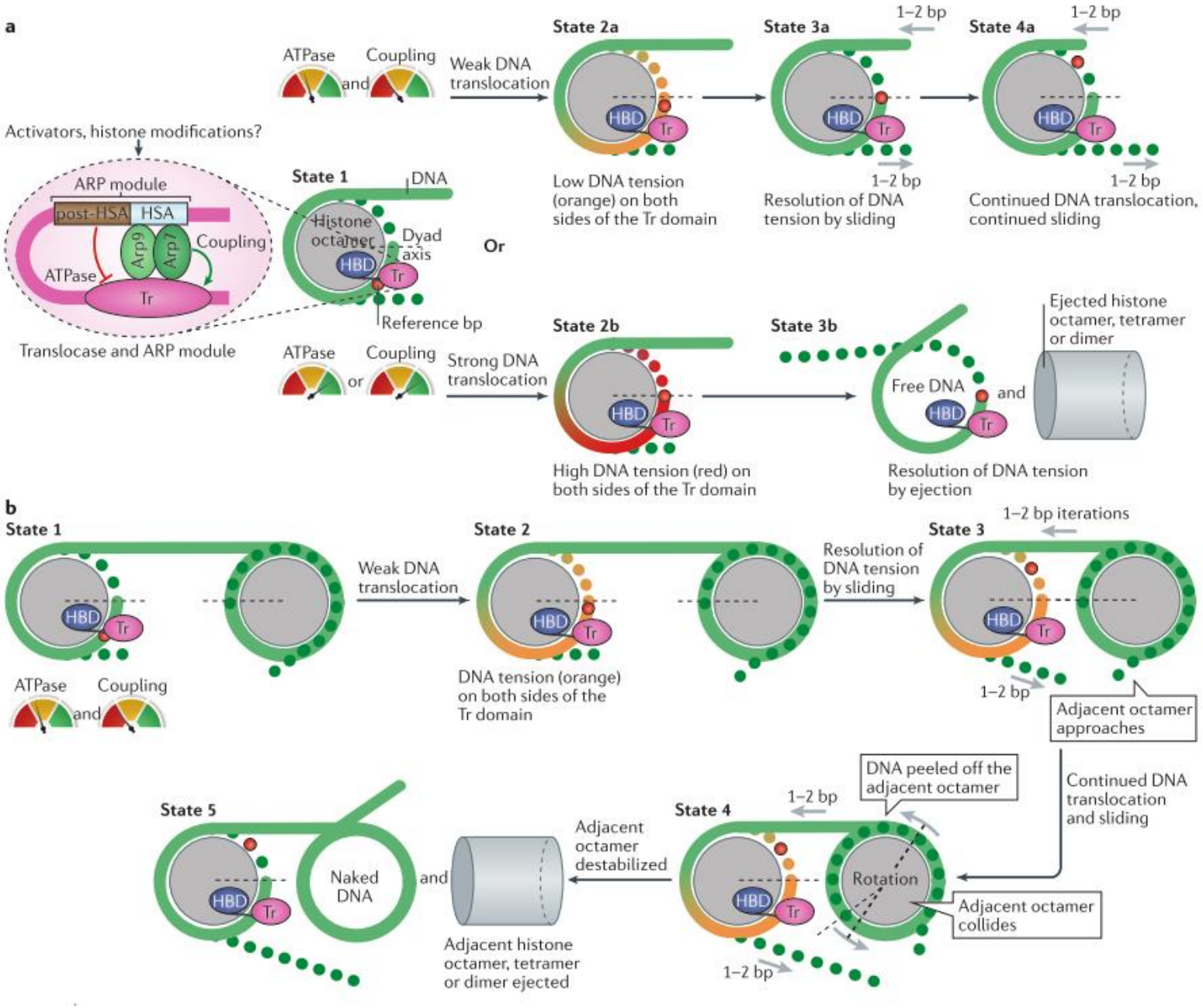
- ISWI - HAND–SANT–SLIDE (**HSS**) domain that binds the unmodified histone H3 tail and the linker DNA flanking the nucleosome. NegC regulates the activity of ATPase domain.
- CHD – two tandemly arranged **chromodomains** (chromatin organization modifier). DNA-binding domain (**DBD**) comprised of only the SANT and the SLIDE domains.
- SWI/SNF – helicase/ SANT-associated (**HSA**) domain that binds actin and/or actin-related proteins, AT-hooks and bromodomain
- INO80 – contain a variable, large **insertion** between lobes. **HSA** domain nucleates actin and ARPs (found in SWR1)



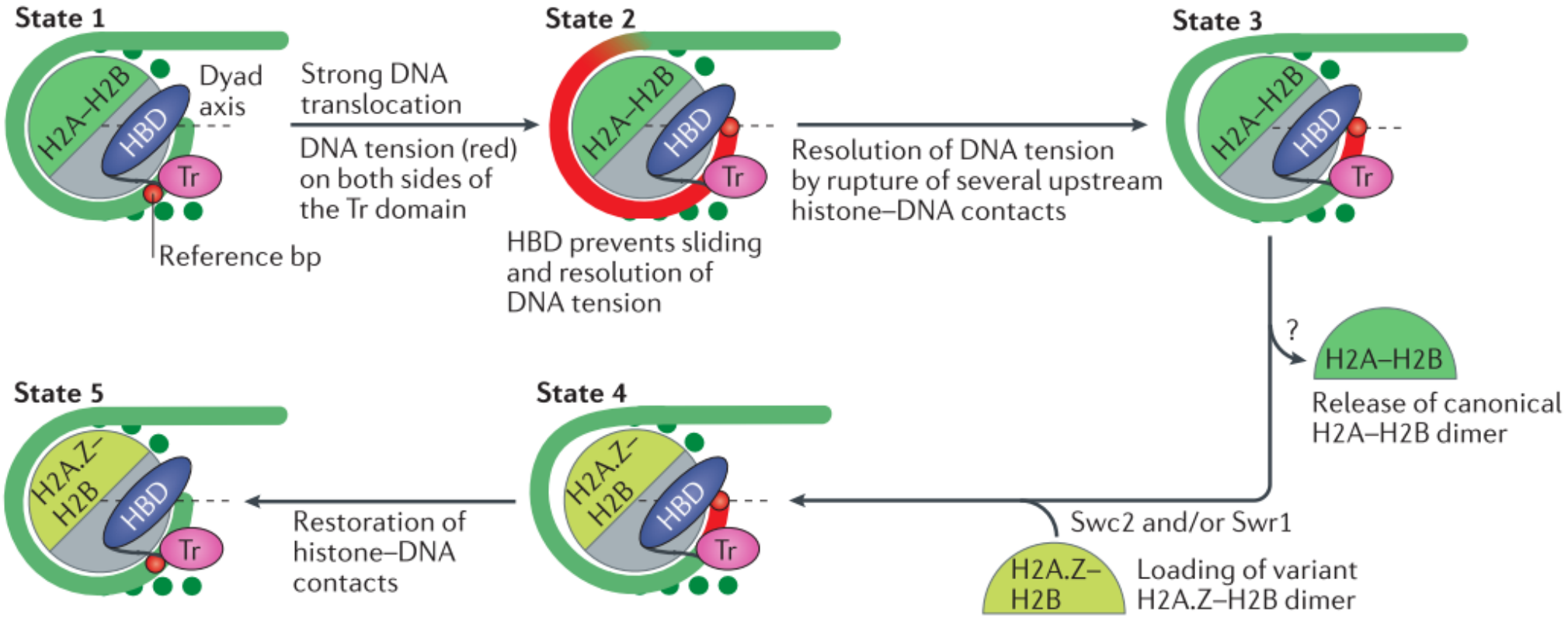
Model of nucleosome spacing by ISWI subfamily remodelers



Models of nucleosome ejection by SWI/SNF subfamily



Model of histone exchange by the remodeler SWR1C



RESEARCH ARTICLE

CHROMATIN

Distortion of histone octamer core promotes nucleosome mobilization by a chromatin remodeler

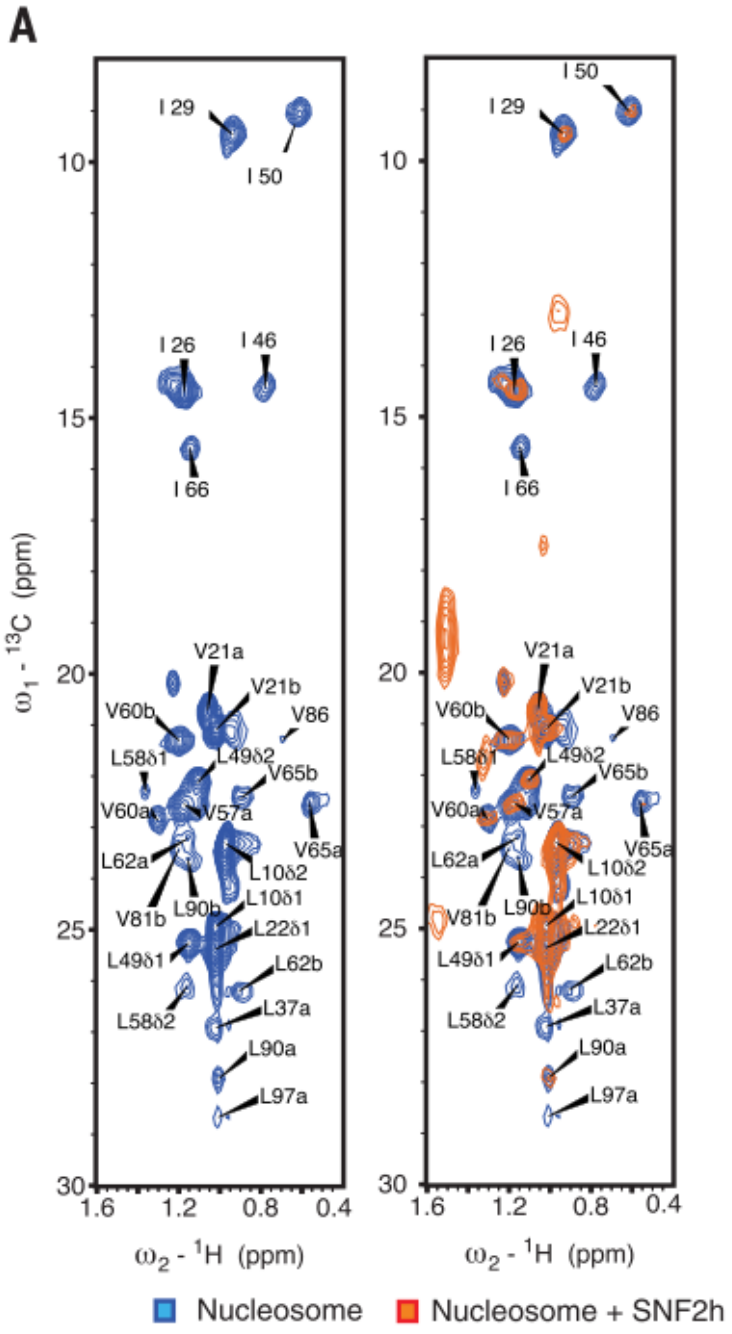
Kalyan K. Sinha,[1] John D. Gross,[2]* Geeta J. Narlikar[1]*

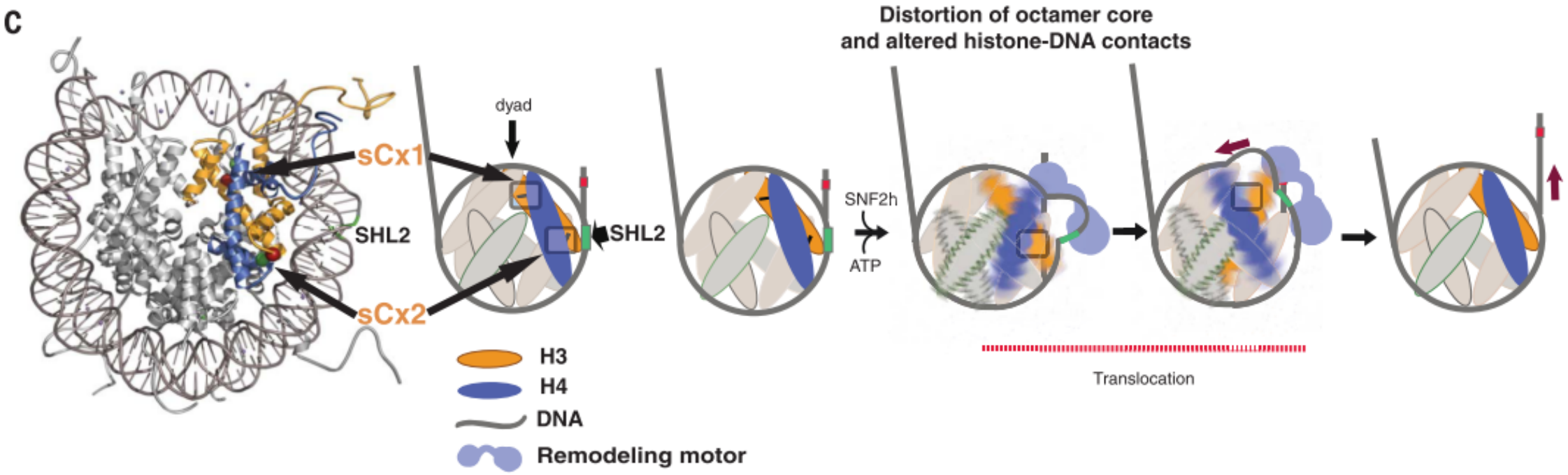
Adenosine 5′-triphosphate (ATP)–dependent chromatin remodeling enzymes play essential biological roles by mobilizing nucleosomal DNA. Yet, how DNA is mobilized despite the steric constraints placed by the histone octamer remains unknown. Using methyl transverse relaxation–optimized nuclear magnetic resonance spectroscopy on a 450-kilodalton complex, we show that the chromatin remodeler, SNF2h, distorts the histone octamer. Binding of SNF2h in an activated ATP state changes the dynamics of buried histone residues. Preventing octamer distortion by site-specific disulfide linkages inhibits nucleosome sliding by SNF2h while promoting octamer eviction by the SWI-SNF complex, RSC. Our findings indicate that the histone core of a nucleosome is more plastic than previously imagined and that octamer deformation plays different roles based on the type of chromatin remodeler. Octamer plasticity may contribute to chromatin regulation beyond ATP-dependent remodeling.

Main question

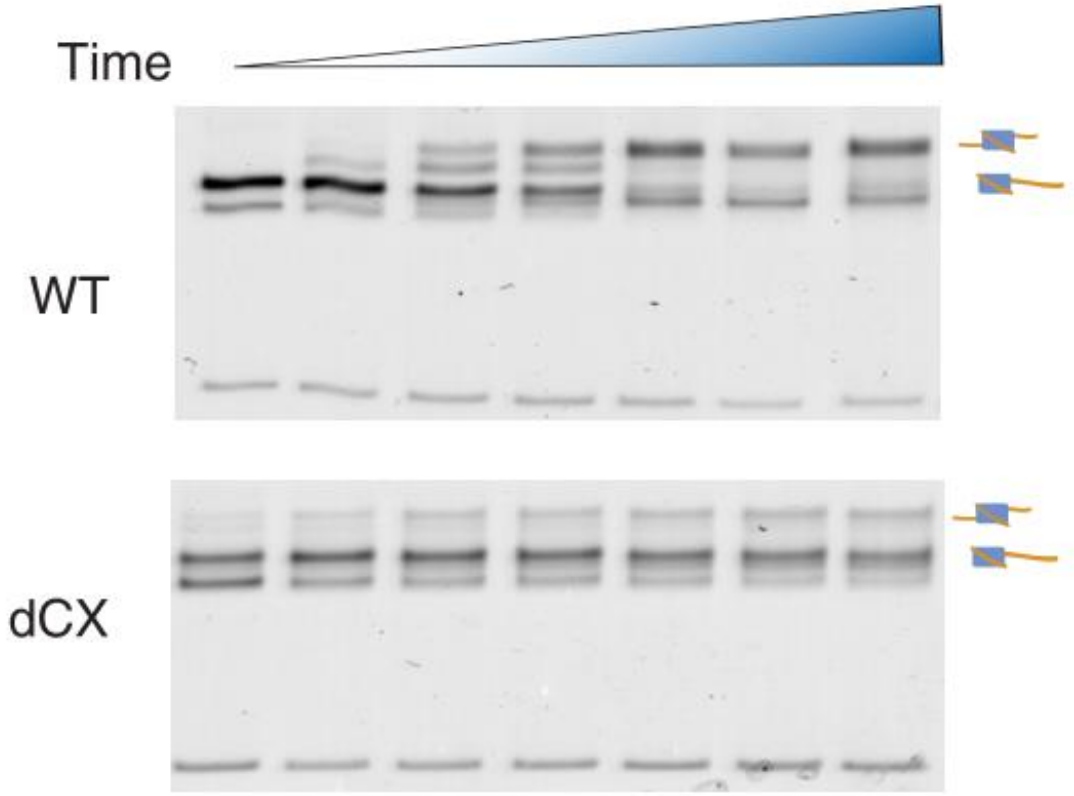
- ~7 bp of DNA is translocated from SHL2 *toward* the dyad and eventually out from the exit side *before* any DNA is translocated *inward* from the entry site

- Methyl-TROSY spectrum of nucleosome bound to SNF2h
- 1H-13C transverse relaxation-optimized nuclear magnetic resonance spectroscopy

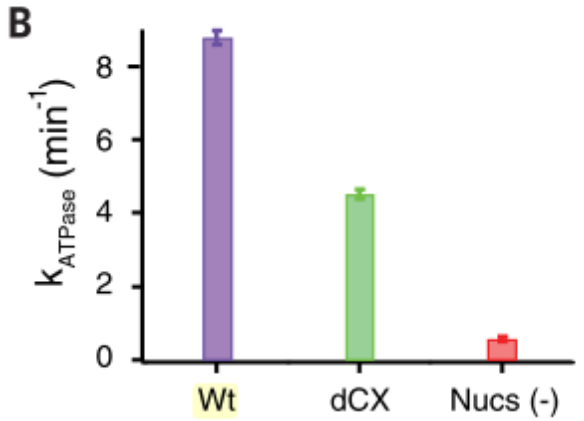


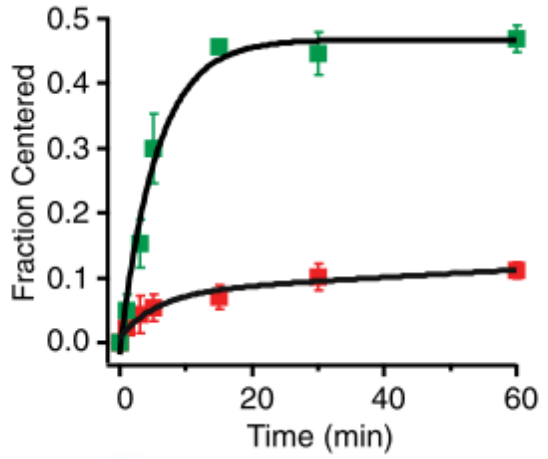


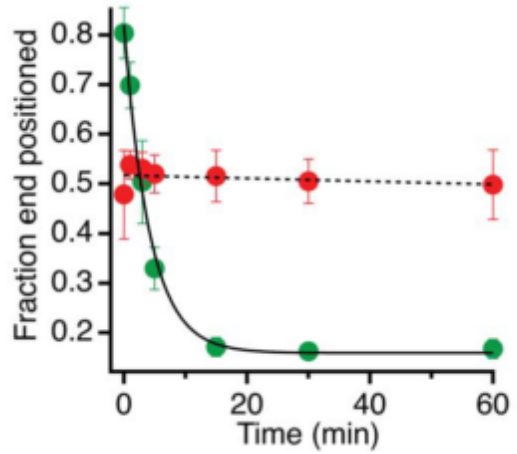
the DNA end as seen previously (*47*). (**C**) Model for role of octamer distortion in DNA mobilization by SNF2h. Histone octamer deformation proximal to SHL2 is coupled to translocation from SHL2 while deformation proximal to the dyad enables movement may allow the nucleosome to accommodate less DNA, thereby preventing the accumulation of any strain in the structure. These coupled conformational changes lead to a net translation of DNA from the exit site before any DNA is drawn in from the entry site. The location of the sCx1 and sCx2 cross-links is highlighted by the gray rectangles. The dashed lines in (B) are straight lines drawn through the data because the changes were too small to fit with an exponential.



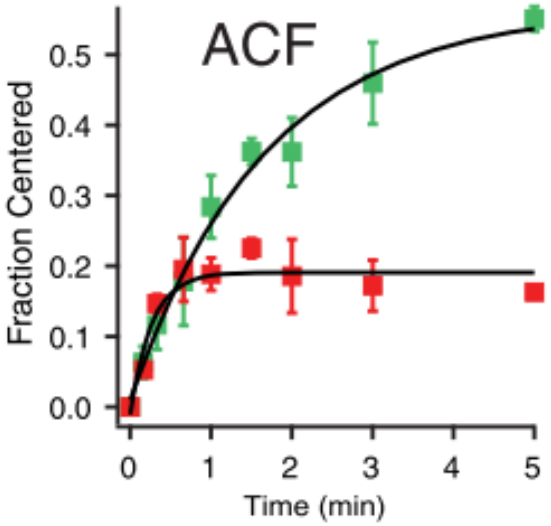
- WT – wild type
- dCX - red

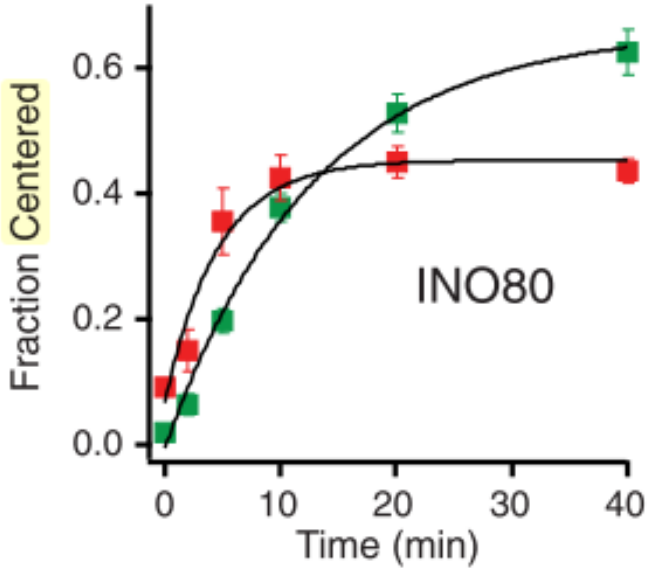


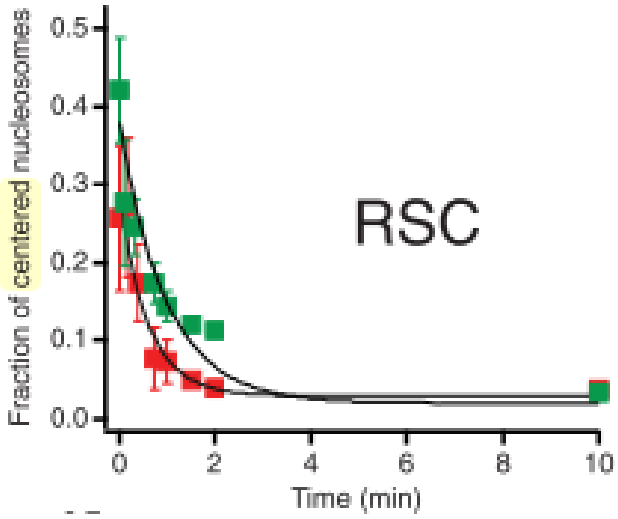


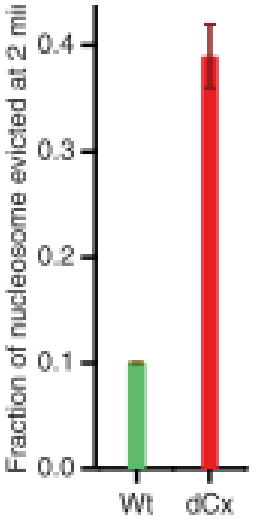


Other remodelers









- Simplest model: nucleosome-stimulated ATP hydrolysis generates an *intermediate* in which DNA deformation is *thermodynamically coupled* with octamer deformation.
- Deformation of DNA by SNF2h would stabilize deformation of the octamer and correspondingly, deformation of the octamer would promote deformation of DNA by SNF2h -> there are 2 possibilities:
- octamer deformation could arise indirectly as a result of changes propagated from remodeler-DNA interactions;
- the octamer could be directly deformed by SNF2h

Implications

- How other remodeler families use the DNA plasticity?
- How many conformations an octamer has?
- Other things that can stabilize histone conformation
- New models of many molecular processes