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Structure and Function of SWI/SNF Chromatin Remodeling Complexes and Mechanistic Implications for Transcription

Liling Tang[‡,¥], **Eva Nogales**[$,£,†,§], and **Claudio Ciferri**[†,§]

[‡]Key Laboratory of Biorheological Science and Technology (Chongqing University), Ministry of Education Chongqing, China 400044

[¥]College of Bioengineering, Chongqing University, Chongqing, China 400044

[$]Life Sciences Division, Lawrence Berkeley National Lab, Berkeley, CA, USA

[£]Howard Hughes Medical Institute

[†]Department of Molecular and Cell Biology, University of California, Berkeley, CA, USA

Abstract

ATP-dependent chromatin remodeling complexes are specialized protein machinery able to restructure the nucleosome to make its DNA accessible during transcription, replication and DNA repair. During the past few years structural biologists have defined the architecture and dynamics of some of these complexes using electron microscopy, shedding light on the mechanisms of action of these important complexes. In this paper we review the existing structural information on the SWI/SNF family of the ATP dependent chromatin remodeling complexes, and discuss their mechanistic implications.

Keywords

: Chromatin; Remodeling; SWI/SNF; Structure

Introduction

Cells have developed several mechanisms to manipulate DNA and tightly package it into chromatin. The building block of chromatin is the nucleosome, which comprises 147 base pairs of DNA wrapped around an octamer of core histones H2A, H2B, H3 and H4 (Luger et al. 1997; Kornberg R. 1974). DNA-wrapped nucleosomes assume a spacing of approximately 10-90 bp along the DNA strand. Under physiological conditions, nucleosomal arrays condense into a more compacted and higher-ordered structure known as heterochromatin (Thoma et al., 1979; Widom and Klug, 1985).

Although cells utilize this compaction as a convenient way to store large amounts of DNA, at any given time thousands of genes need to be activated or repressed in a coordinated process, and the chromatin must be remodeled to permit these events. Histone modifying enzymes (reviewed in Wang Y et al., 2004) and ATP-dependent chromatin remodeling

[§]To whom correspondence should be addressed: cciferri@berkeley.edu, enogales@lbl.gov.

complexes (reviewed in Saha et al., 2006; Clapier & Cairns, 2009) work in concert to regulate this process. Histone-modifying enzymes recognize and covalently mark (by acetylation, methylation, phosphorylation, ribosylation and ubiquitination) specific residues of the histone tails (Strahl and Allis, 2000). ATP-dependent chromatin remodeling complexes specifically recognize these histones marks, and through ATP hydrolysis unwrap, mobilize, exchange or eject the nucleosome, and subsequently recruiting a transcriptional apparatus to nucleosomal DNA (Figure 1; Owen-Hughes T, 2003; Levine & Tjian, 2003; Cosma MP 2002). In this manner, chromatin structure simultaneously provides a packaging solution and a sophisticated apparatus for regulating gene expression.

ATP-dependent chromatin remodeling complexes are large (>1 MDa) multi-components complexes (consisting of between 4 and 17 subunits) that are highly conserved within eukaryotes. They are characterized by the presence of an ATPase subunit belonging to the superfamily II helicase-related proteins (Singleton & Wigley, 2002). Proteins belonging to this class contain an ATPase domain that is itself comprised of two parts, the DExx and HELICc regions, which are separated by a linker. This class can be further classified into at least 4 different families (SWI/SNF, ISWI, NURD/Mi-2/CHD and INO80) based on the additional presence of unique domains within or adjacent to the ATPase domain (Figure 2). In this review we will explore the function, the architecture, and the structural implication of the nucleosome remodeling activity of the SWI/SNF family of the ATP-dependent chromatin remodeling complexes.

The SWI/SNF family

The SWI/SNF family of chromatin remodeling complexes was initially discovered in yeast by two independent screenings aimed at identifying mutations in genes that affect the mating-type switching (SWI) and sucrose fermentation (Sucrose Non Fermenting - SNF) pathways (Workman and Kingston, 1998; Sudarsanam and Winston, 2000). A genetic screening for suppressive mutations of the SWI/SNF phenotypes identified different histones and chromatin components, suggesting that these proteins were possibly involved in histone binding and chromatin organization (Winston and Carlson, 1992). Biochemical purification of the SWI/SNF2p in *S. cerevisiae* demonstrated that this protein was part of a complex containing an additional 11 polypeptides, with a combined molecular weight over 1.5 MDa. The SWI/SNF complex contains the ATPase Swi2/Snf2p, two actin-related proteins (Arp7p and Arp9) and other subunits involved in DNA and protein-protein interactions. The purified SWI/SNF complex was able to alter the nucleosome structure in an ATP-dependent manner (Workman and Kingston, 1998; Vignali et al., 2000). A closely related complex, named RSC (Remodeling the Structure of Chromatin) was also initially identified in yeast (Cairns et al., 1994). This complex is composed of 17 subunits and shows similarities to the SWI/SNF complex. In particular Sth1, the ATPase component, is the counterpart of SWI2/Snf2p in SWI/SNF, and also comprises the same two actin related proteins, Arp7 and Arp9, and its subunits Rsc6p, Rsc8p and Sfh1p are paralogues of the Swp73p Swi3p and Snf5p components in the SWI/SNF complex (Table 1). Despite these similarities, RSC and SWI/SNF regulate different chromatin regions, the former being required for a larger spectrum of genes. For this reason RSC is more abundant and its function is indispensable for cell survival.

The structures of the SWI/SNF and RSC complexes are highly conserved, although their compositions are not identical, reflecting an increasing complexity of chromatin through evolution. Higher eukaryotes exhibit an increased genome size, the presence of DNA methylation, and more complex genetic organization. For this reason, the SWI/SNF and RSC complexes in higher eukaryotes maintain core components, possibly to maintain

overall shape and remodeling activity, but also substitute or add on other components with more specialized or tissue-specific domains.

The human and drosophila homologous complexes have been extensively characterized biochemically and genetically. As in yeast, these species contain two distinct remodeling complexes homologous to SWI/SNF and RSC, respectively. In drosophila the two complexes are called BAP (Brahma Associated Protein) and PBAP (Polybromo-associated BAP) complexes. In human, similarly, these two complexes are called BAF (Brg1 Associated Factors) and PBAF (Polybromo-associated BAF).

In Drosophila, the BAP and PBAP complexes comprise the same ATPase subunit, named Brahma, equally homologous to both Swi2/Snf2p and Sth1p. They also share the following core components: Moira, Snr1, BAP60, Actin and the Actin Related Protein BAP55, as well as BAP111, a component that has not been identified in yeast, and possibly associated with the presence of higher chromatin complexity in *D. melanogaster* (Table 1).

In human, the BAF complex can contain one of the two distinct ATPase subunits hBRM (human Brahma) or BRG1 (Brahma-related Gene 1). PBAF, instead, only contains the ATPase BRG1. As in drosophila, BAF and PBAF share the different core components BAF47, BAF57, BAF60, BAF155, BAF170, BAF45 and the two actins b-Actin and BAF53 (Mohrmann and Verrijzer, 2005; Wu et al., 2008).

In drosophila and human the two remodeling complexes are characterized by unique components that indicate homology to either ySWI/SNF or yRSC complex. In particular the BAP and BAF complexes contain the DNA binding protein OSA/BAF250, homologous to Swi1, indicating that the BAP and BAF complexes are homologous to SWI/SNF. PBAP and PBAF themselves comprise the DNA binding protein BAP170/BAF200 homologue to the yeast RSC9 and Polybromo (BAP180/BAF180), a protein important for the binding of acetylated histones, structurally related to the yeast components Rsc1, Rsc2 and Rsc4. In addition, Brd7, another bromodomain-containing protein is also part of the human PBAF complex (Kaeser et al., 2008).

Interestingly, in transitioning to vertebrates, the increasing genome size also corresponds to the introduction of gene families. This gives the ability to assemble different complexes specific to a developmental stage, or to specific organs. It is important to note that in humans BAF60, BAF45, BAF53 and BAF250 exist in different isoforms and are coded from different genes, but only one of these can be incorporated into a specific tissue or cell-specific remodeling complex.

In summary, eukaryotic cells have two subfamilies of SWI/SNF chromatin remodeling complexes, differentiated by the presence of the signature components: SWI/SNF/BAP/BAF and RSC/PBAP/PBAF complexes.

Domain Organization of the SWI/SNF Remodeling Complexes

SWI/SNF and RSC complexes contain within their components different protein-protein or protein-DNA interaction modules, which cooperate to achieve the nucleosome remodeling activity. Given the homology between different species, here we focus on the domain composition and organization of the human BAF and PBAF complexes (Figure 3). The central core, as reported previously, is the ATPase catalytic subunit BRG1/hBRM. This subunit, apart from the HELICc and DExx catalytic domains, also contains four protein-protein interacting modules. It shows a QLQ domain, important for protein-protein interaction (Kim et al., 2003), a HSA domain, involved in the binding of beta actin and the actin related protein BAF53 a,b (Szerlong et al., 2008), a BRK domain, of unknown function

and a bromodomain, a four-helix bundle motif important for the binding of acetylated histones (Haynes et al., 1992). PBAF also contain two other bromodomain-containing proteins: BRD7 and Polybromo (BAF180). BRD7 contains a single bromodomain, while Polybromo contains six bromodomains, each of them important to recognize a specific acetylation of the Histone H3 (Thompson M, 2009). Polybromo also shows two Bromo Adjacent Homology (BAH) domains, still of unknown function, and a High Mobility Group (HMG) domain, a highly conserved protein fold able to contact the minor groove of DNA introducing a sharp bend (Thomas JO, 2001). The same HMG domain is also present in BAF57. This subunit also contains a coiled coil region that appears too be important for homodimerization and for the binding of the coiled coil region of BAF155/BAF170 subunits (Chen and Archer, 2005; Ciferri and Nogales, unpublished). BAF155 and BAF170 are protein scaffolds important for the assembly of many components of the BAF and PBAF complexes (Chen and Archer, 2005). They also contain the CHRomatin Organization MOdifier (CHROMO) domain, a 60aa motif important for chromatin targeting (Koonin et al., 1995) and the SANT domain, a sequence specific DNA binding module (Biedenkapp et al., 1988).

BAF200 and BAF250 are two DNA binding protein able to interact with AT rich DNA region using their BRIGHT domain (Kortschark et al., 2000). BAF200 also contain two canonical Zn finger C2H2 domains important in sequence-dependent DNA binding, as well as protein-protein interaction.

Two similar domains are also contained in BAF45 (Lessard et al., 2007). It comprises a double PHD domain (C4HC3 Zn Finger). The PHD domain has been found in other complexes to be involved in protein-protein interactions.

In summary all the SWI/SNF components comprise protein-protein or DNA binding domains important for chromatin targeting and the remodeling process. Some of the protein-DNA binding motifs show a “histone-like” folding. They are used to facilitate the displacement of the DNA during the nucleosome remodeling as described in the next section.

SWI/SNF dependent Nucleosome Remodeling Mechanism

Chromatin remodeling complexes use the energy of ATP hydrolysis to slide the DNA around the nucleosome (Figure. 4). The first step consists in the binding between the remodeler and the nucleosome. This binding occurs with nanomolar affinity (Lorch et al., 1998) and reduces the digestion of nucleosomal DNA by nucleases (Saha et al. 2005).

Based on single molecule experiments (Zhang et al., 2006), the translocase domain, which has been proposed to be composed of a torsion subdomain and a tracking subdomain, binds a specific location of the nucleosomal DNA situated at approximately two turns from the dyad (Figure 3). Upon ATP hydrolysis, the torsion subdomain carries out a directional DNA translocation (Havas et al., 2000). This event destroys histone-DNA contacts and creates a transient DNA loop that propagates around the nucleosome and resolves when it reaches the exit site on the other side of the nucleosome resulting in nucleosome repositioning. The tracking domain ensures that the waves of DNA loops can move only in one direction blocking any backward movement. The remodeler then resets its original position ready for a new remodeling cycle.

It is still unknown if relatively small (1-12 bp) or large loops (>100bp) are formed during remodeling, but we know that during the remodeling process the contacts between histones and DNA need to be broken and reformed along the length of the nucleosome. The dynamics of these interactions are likely to diminish the barrier of energy that the

remodeling needs to overcome in order to slide the nucleosome. A similar mechanistic principle should apply during phenomena such as histone ejection by SWI/SNF in the presence of histone chaperones (Lorch et al., 2006; Boeger et al., 2003).

In the next section we will explore the published structures of the SWI/SNF and RSC complexes and analyze their properties to shed light of this mechanism.

Structures of the SWI/SNF Chromatin Remodeling Complexes

Understanding the structural details by which the SWI/SNF and RSC complexes engage and remodel the nucleosome is one of the open questions in the field of gene regulation. Because of the dimensions, flexibility and the difficulties in obtaining a large amount of sample, electron microscopy and 3D reconstruction have been the structural technique of choice. During the last few years, different structures of the SWI/SNF and RSC complexes have been proposed from different labs.

The first structure to be solved was that of the yeast RSC complex (Asturias et al., 2002). This complex was purified from endogenous sources (Cairns et al., 1996) and imaged using negative stain electron microscopy (Asturias et al., 2002). This work showed the RSC complex to have dimensions of 250 Å by 150 Å. The structure appears composed of four globular domains arranged around a central cavity. Three of the domains are arranged in an upper platform and a lower domain, connected to the upper part through a flexible hinge, pivots between a close conformation (if collapsed towards the other three domains) or an open conformation. In the open conformation, the lower domain is connected only on one side and the complex assumes a C shape with a cavity proposed to be sufficiently big to accommodate a nucleosome. This structure, obtained by Random Conical Tilt (RCT), showed preferential orientation and likely flattening, making it difficult for the authors to use it as an initial model for structure determination by Cryo-Electron Microscopy.

In the same study, the authors also attempted to obtain the structure of the RSC complex bound to the nucleosome. When equimolar amount of RSC and nucleosome were incubated together the authors were able to see some additional density in the central cavity, indicating that this might be the site of nucleosome engagement.

About the same time another study (Smith et al., 2003) reported the negative stain, 3D reconstruction of the yeast SWI/SNF complex using by Angular Reconstruction. The complex showed an ablate shape of 250 Å by 120 Å, with multiple small lobes surrounding a shallow depression, which was proposed to serve as the nucleosome binding site.

A few years later, a 3D reconstruction of the human RSC complex (PBAF), purified from endogenous material from HeLa cells (Lemon et al., 2001), was reported (Leschziner et al., 2005). This study also used negatively stained sample and the structure was determined using the RCT technique. Overall the human PBAF structure appeared similar to the yeast RSC structure, but very distinct from the yeast SWI/SNF one. PBAF has a C-shaped architecture surrounding a central cavity and contains a platform region that resembles the three lobe architecture of the upper portion of the RSC structure. From this platform, as for the RSC structure, there is a Knob (defined as K1) that can assume different conformations and that resembles the flexible lower domain observed for the yeast RSC structure. The authors tried to solve the structure of the complex bound to the nucleosome and although the occupancy was not full, it was clear, from some of the 2D class averages, that the nucleosome was located inside the central cavity. This aspect reinforced the similarity between the structures of the human PBAF and the yeast RSC complex.

Since these initial studies, another two structures of the yeast RSC complex were almost simultaneously onbtained in the Walz and Nogales Labs (Skiniotis et al., 2007, Leschziner et al., 2007).

Starting from the observation that in yeast, all the bromodomain containing proteins, involved in the binding of acetylated lysines, were segregated, almost exclusively, in the RSC complex (Rsc1, Rsc2 and Rsc4 subunits), Skiniotis and colleagues investigated whether the recognition and the binding of acetylated lysine was a crucial mechanism for the remodeling mechanism. To this end, they solved the structure by negative staining of the RSC remodeler in complex with different Histone H3 peptides by RCT (Skiniotis et al., 2007). The structures obtained were really similar to that proposed before by Asturias and colleagues, with an upper three lobe structure connected on one side to a flexible lower lobe that could assume an open and a close conformation. Interestingly, upon binding of an acetylated Histone H3 peptide modified at K9 or K14, the RSC complex was assuming almost entirely a close conformation. This was not occurring if a non acetylated, a methylated, or an acetylated peptide with a random sequence were used, indicating that the acetylation and the sequence specificity was really important for engaging the binding between RSC and Histone H3. In addition, this conformational change was independent from the presence of ATP, indicating that the peptide binding was necessary and sufficient for this conformational change. Unfortunately, given the size of the peptide, it was impossible to localize the binding site for the acetylated Histone H3 on the RSC complex.

All the structures presented so far were determined by Random Conical Tilt or Angular Reconstitution methods. Both these techniques have limitation. In particular, the Angular Reconstitution Technique assumes that the different images of the complex represent different views of the same object. This is not really true for flexible complexes undergoing severe conformational changes, as appears to be the case for these remodeling complexes. The limit in the use of the Random Conical Tilt technique is the presence of a missing cone of data due to the geometry of the data collection that results in an anisotropic reconstruction. While this problem may be overcome by appropriately combining RCT reconstructions from complexes that had different orientations on the grid, both of the RSC structures described so far, as well as the PBAF one, suffered from a single preferential orientation.

In order to avoid these limitations, Leschziner and Nogales introduced a new method, known as OTR (Orthogonal Tilt Reconstruction, Leschziner and Nogales, 2007) in which data collection at −45 and +45 degrees results in individual volumes with a full sampling of angles. This method eliminates the missing cone artifact and the only requirement is that the sample orients on the grid in many different conformations so that the sampling at different degrees will be complete.

Using this geometry-based technique, and reducing preferential orientation and flattening by control blotting of the stain, Leschziner and colleagues determined two new structures of the yeast RSC complex, in the open and closed conformations (Leschizner et al., 2007). These structures resemble the two RSC and the PBAF structures previously determined in the Asturias, Walz and Nogales laboratories, respectively, but show increased 3-dimensionallity. While the previous reconstructions were well defined in one direction, they appeared as cut-outs in the poorly define direction, likely due to a combination of missing cone and flattening effects. The OTR structures of RSC show a well-defined cavity with great shape complementarity to the nucleosome (Figure 5). Comparison of the two OTR RSC structures shows significant movement of the lid and arm regions, movements likely relevant to allow the binding of the nucleosome, and also in the remodeling process.

The first Cryo-EM structure of the yeast SWI/SNF complex was published in 2008 (Dechassa et al., 2008). This reconstruction was very similar to the one obtained previously using negative stain, but appeared less flat. In this paper, the authors took advantage of DNA footprinting and photoreactive site-specific cross-linking to identify regions of the nucleosome directly bound to the SWI/SNF complex. DNA footprinting data showed that the SWI/SNF complex makes close contacts with only one gyre of nucleosomal DNA. Protein crosslinking showed that the ATPase SWI2/SNF2p and Swi5p (the homologue of Ini1p in human), Snf6, Swi29, Snf11 and Sw82p (not conserved in human) make close contact with the histones. The SWI/SNF reconstruction reveals a large interaction between the nucleosome and the remodeling complex. This organization might cause a more severe destruction of the histone-DNA binding remodeling the nucleosome in larger steps or being responsible for nucleosome ejection by lowering the energy barrier and therefore allowing the histone chaperones to remove the dimmers or the whole octamers. Given the low conservation of some of the components in higher eukaryotes, it is difficult to predict if the mechanism of SWI/SNF nucleosome interaction and remodeling is fully conserved in all the species.

In late 2008 Asturias and colleagues presented a Cryo-EM reconstruction of the yeast RSC complex in a nucleosome bound state (Chaban et al., 2008). A comparison between the structure of the unbound RSC and RSC-nucleosome complex shows an additional mass in the central cavity. The authors comment that, despite the presence of additional density in the central cavity, the shape of this density did not match the one of the nucleosome but only of the histones octamer indicating that the DNA upon nucleosome binding might assume a poorly ordered conformation. Because the RSC-Nucleosome dataset was collected in the absence of ATP, under conditions where no DNA loop propagation can occur, the authors proposed that the interaction between RSC and the nucleosome might alter the DNA-histone binding resulting in the change of the nucleosome structure. On the other end, the authors also noticed that the density of Histone H2A-H2B dimer was only partially resolved possibly because of the limited resolution of the Cryo-EM reconstruction and that the fit of the histones in the central density was not perfect indicating that the missing density reported from the DNA might also just be due to the quality of the data, the threshold used or the data processing procedure.

All the structures presented in this review, despite the different technique and imaging reconstruction method used, reveal detail and interpretation for the mechanistic studies. A common feature is the presence of a large cavity (or surface for the SWI/SNF) able to interact with the Nucleosome, although its placement is only amenable by molecular modeling. This cavity can only accommodate small waves/loop (<20bp) propagation. The presence of larger loops will create clashes unless they would occur in regions where the nucleosomal DNA is accessible to solvent, like the exposed dyad. Alternatively, severe conformational changes need to be expected from these complexes in order to accommodate larger loop propagation around the nucleosome.

Concluding remarks

Despite the huge amount of genetic, biochemical and structural biology data published during the last several decades, the mechanism by which ATP dependent remodeling complexes recognize, bind and remodel the nucleosome is still far to be completely understood. High-resolution structure determination will certainly be invaluable for understanding this process in mechanistic detail. Given the dimensions, the complexity and the flexibility of these complexes, high-resolution cryo-EM would definitely be the method of choice. The introduction of automatic data collection (Potter et al., 1999) and the use of Maximum Likelihood data processing (Scheres et al., 2005) are promising new

breakthroughs for the collection and analysis of larger datasets, that may help resolving different complex conformations and ultimately an improvement of the quality and resolution of the structures. Subnanometer structure resolution for asymmetric complexes by Cryo-EM has become recently achievable. Immuno-labeling and/or protein tagging may also contribute to our mechanistic understanding of these complexes by allowing the localization of each of the component within the overall architecture.

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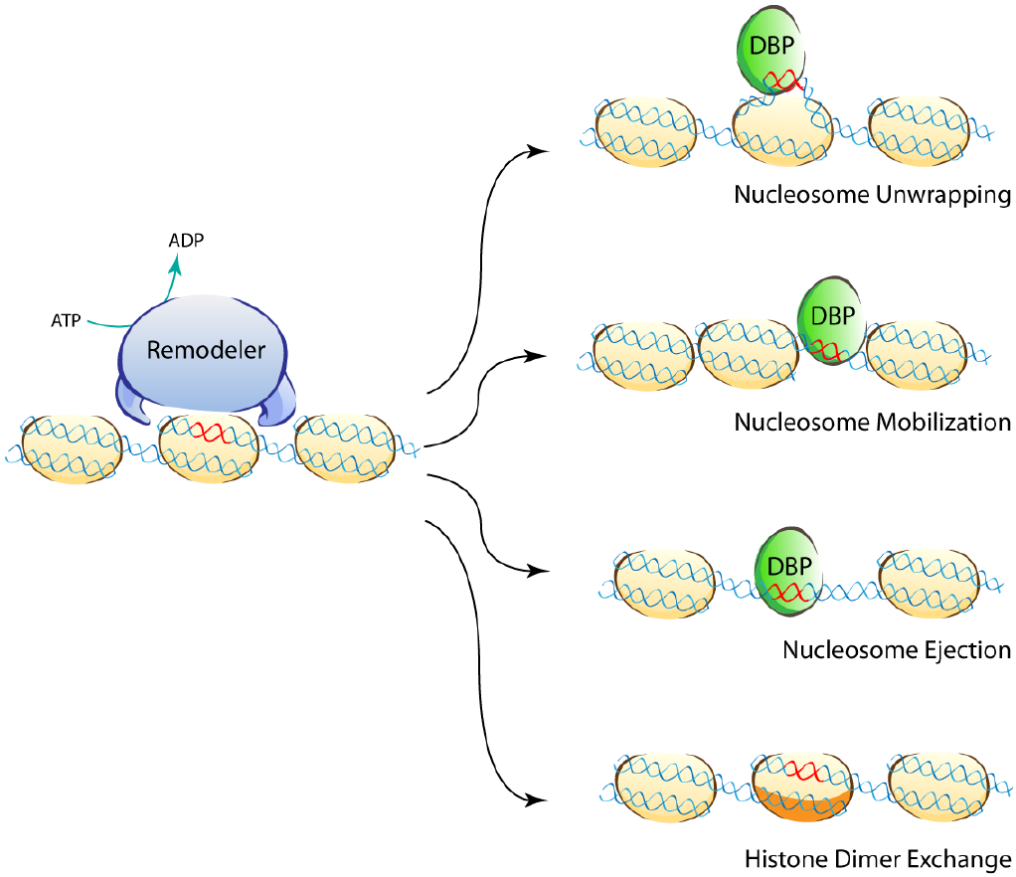

Figure 1.
Different effects of the ATP dependent chromatin remodeling activity of remodelers on nucleosomal DNA: upon hydrolysis of ATP, a protected region of chromatin can become available to DNA binding protein complexes, such as transcription factors (in green). Nucleosomes can be unwrapped, mobilized or ejected to allow these processes. In some cases ATP dependent remodeling complexes can use ATP to introduce histone variants within the nucleosome by a process called dimer exchange. (DBP stands for DNA-binding protein)

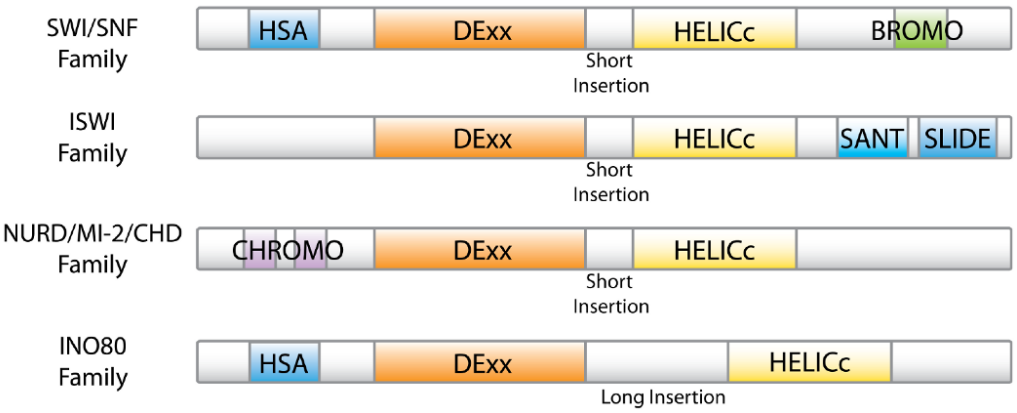

Figure 2.

Classification of ATP-dependent chromatin remodeling complexes: The ATPase subunit of all the remodeling complexes belongs to the superfamily II helicase group. The ATPase always contains a DExx and a HELICc domain, spaced by a linker. The remodelers are classified into different families based on the presence of additional domains on their ATPase subunits. The SWI/SNF family contains a HSA domain, involved in actin binding, and a bromodomain important for the binding of acetylated lysines. The ISWI family contains the SANT and SLIDE domains, important for histone binding. The CHD/NURD/Mi-2 family contains a tandem Chromo domain, also used for histone binding. The INO80 family, like the SWI/SNF family, comprises a HSA domain but it is also characterized by the presence of a longer insertion between the DExx and the HELICc domains.

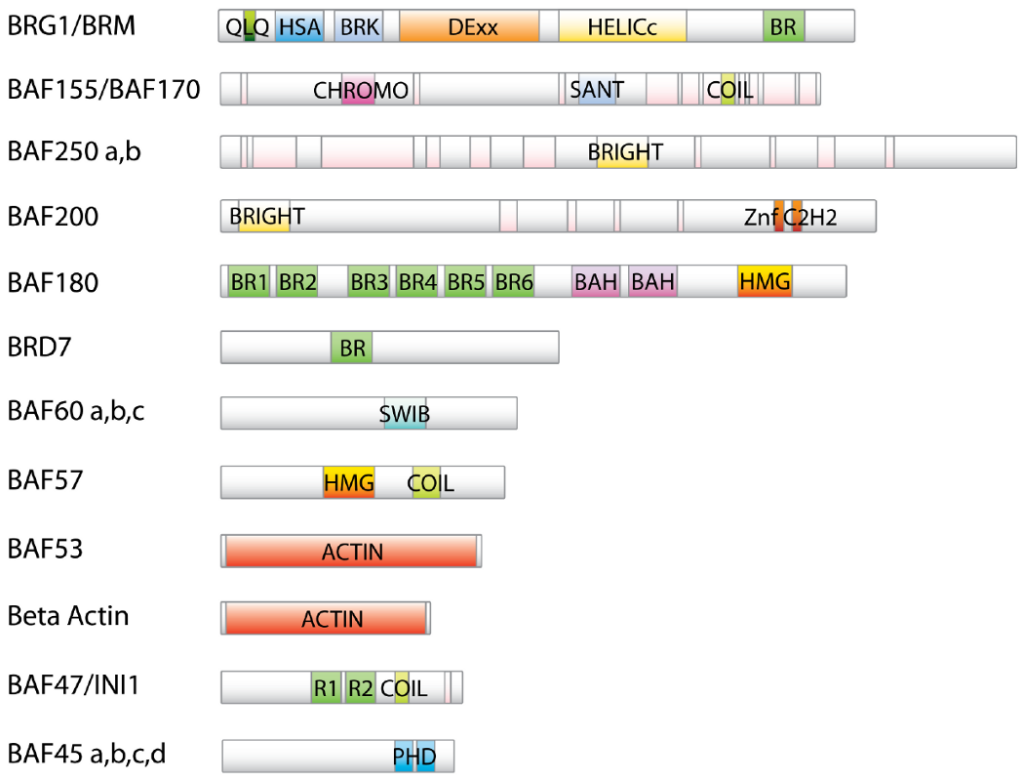

Figure 3.
Prediction of the domain architecture of the human BAF and PBAF components. Proteins and domains are approximately in scale. Unlabeled pink modules indicate low complexity regions.

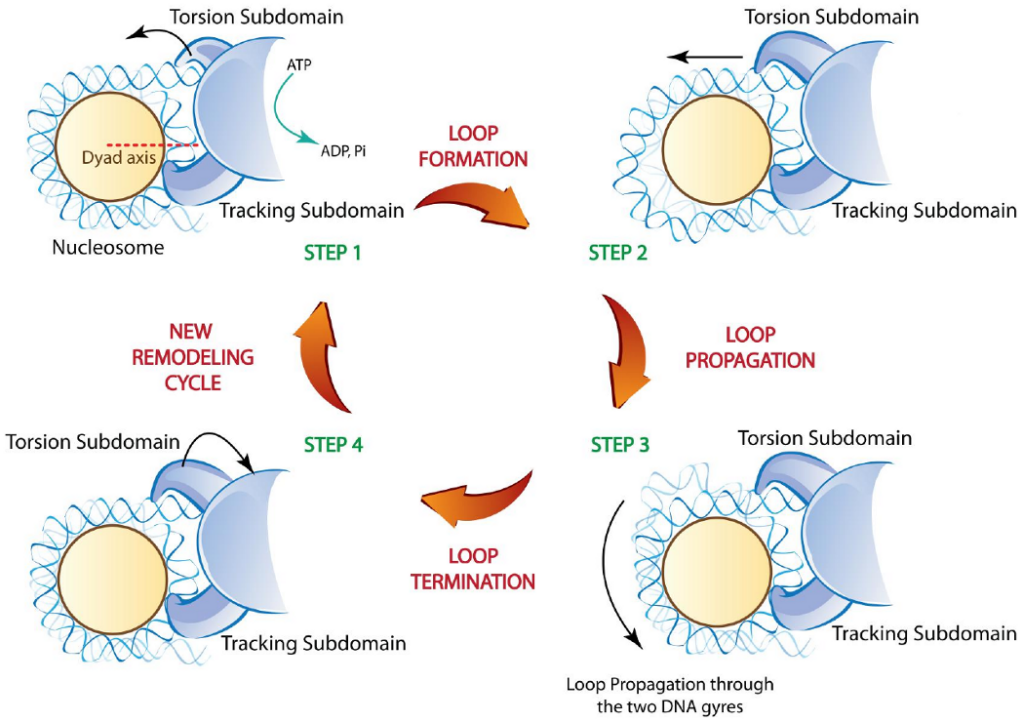

Figure 4.

Schematic representation of the SWI/SNF dependent nucleosome remodeling process. The nucleosome is illustrated as spherical disc surrounded by the two DNA gyres (indicated with two different brightness based on the relative distance to the reader). Steps 1-4 indicate the different stages proposed to occur during the remodeling process. During Step1, the translocase domain binds the nucleosome two turns away from the dyad. Upon ATP-dependent hydrolysis, the torsion sub-domain generates a DNA loop that translocates through the tracking subdomain and the dyad, continuing in the second gyre (Step 2-3). The loop resolves when it reaches the exit site on the other side of the nucleosome (Step 4). The combination of these steps results in nucleosome repositioning. The complex is then ready for a new remodeling cycle (Step1).

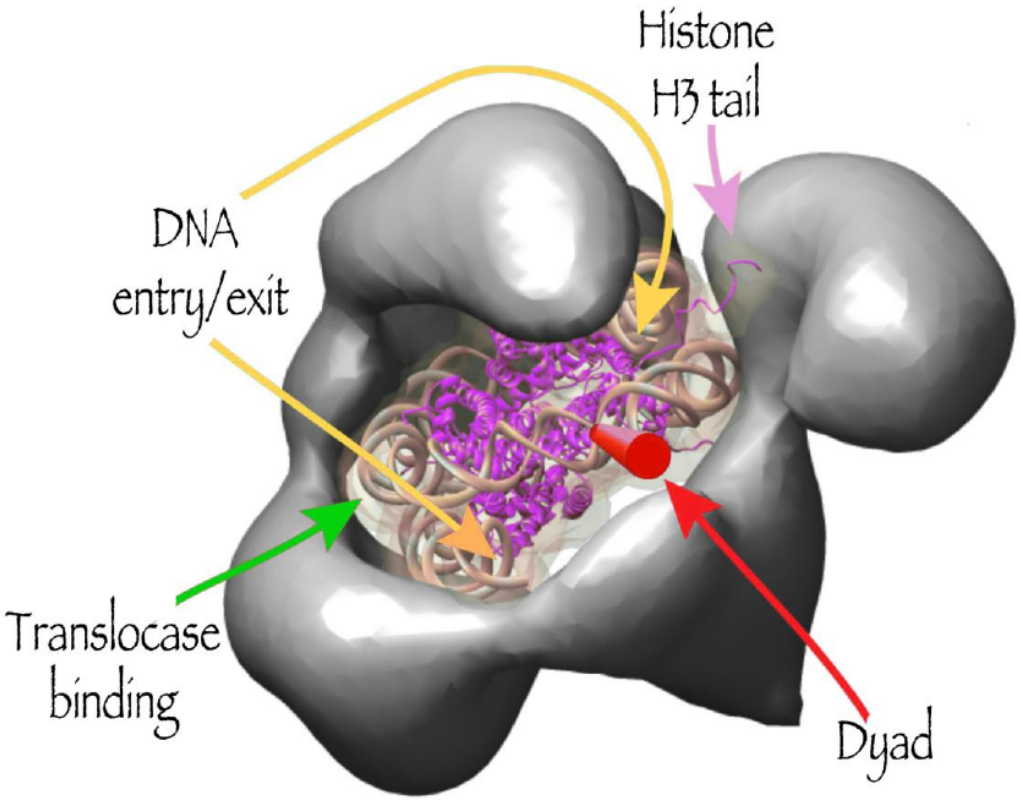

Figure 5.
Functional model of nucleosome binding shown on the OTR reconstruction of the yeast RSC complex. Redrawn from Leschziner et al., 2007.

TABLE1

Conservation of SWI/SNF and RSC components during the evolution.

	ORGANISM					
	S. *cerevisiae*		*D melanogaster*		*H sapiens*	
COMPLEX	**SWi/SNF**	**RSC**	**BAP**	**PBAP**	**BAF**	**PBAF**
	Swi2/Snf2	Sth1	BRM/Bhrama		BRG1 or hBRM	BRG1
	Swi3	Rsc8/Swh3	MMOIRA/BAP155		BAF155/BAF170	
	Swi1/Adr6		OSA		BAF250a,b	
		Rsc9		BAP170		BAF200
		Rscl,2,4		Polybromo		BAF180
	Swp73	Rsc6	BAP 60		BAF60 a,b,c	
	Snf5	Sfhl	BAP45/SNR1		INI1/BAF47/hSNF5	
			BAP 111		BAF57	
					BAF45 a,b,C,d	
	Arp 7,9		Actin		beta Actin	
			BAP55/BAP47		BAF53 a,b	
						BRD7
	Swp82					
	Snf6					
	Snf11					
	Taf14					
		Rsc3-5,7				
		Rsc10,30				
		Htl1				
		Ldb7				
		Rtt102				

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