Chromatin remodeling by ATP-dependent molecular machines

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Summary

The eukaryotic genome is packaged into a periodic nucleoprotein structure termed chromatin. The repeating unit of chromatin, the nucleosome, consists of DNA that is wound nearly two times around an octamer of histone proteins. To facilitate DNA-directed processes in chromatin, it is often necessary to rearrange or to mobilize the nucleosomes. This remodeling of the nucleosomes is achieved by the action of chromatin-remodeling complexes, which are a family of ATP-dependent molecular machines. Chromatin-remodeling factors share a related ATPase subunit and participate in transcriptional regulation, DNA repair, homologous recombination and chromatin assembly. In this review, we provide an overview of chromatin-remodeling enzymes and discuss two possible mechanisms by which these factors might act to reorganize nucleosome structure. ***BioEssays*** **25:1192–1200, 2003.**

Introduction

In the eukaryotic nucleus, DNA is assembled into a periodic nucleoprotein complex termed chromatin.[1] The repeating unit of chromatin is the nucleosome. In the nucleosome, ~146 bp of DNA is wrapped about two times around a core histone octamer that consists of two copies each of histones H2A, H2B, H3 and H4.[2] A linker histone, such as H1, interacts with the nucleosomal core as well as the adjoining linker DNA. Then, arrays of nucleosomes fold into higher-order structures that range from the 30 nm diameter chromatin filament during interphase to the highly compacted metaphase chromosome during mitosis.

Every nuclear process that requires access to DNA functions in the context of chromatin. The cell has developed multiple strategies for the optimal use of chromatin as the substrate for DNA-directed processes. For instance, histones are covalently modified, such as by acetylation, phosphorylation, methylation, and ubiquitination, to alter the biochemical properties of chromatin as well as to provide signals that regulate the activities of other factors (i.e., 'histone code') (see, for example, Refs. 3,4). Also, histone variants (for example, H2A.Z and H3.3; Refs. 5,6) and/or non-histone chromosomal proteins (for example, high mobility group proteins and heterochromatin protein HP1; Ref. 7) are incorporated to modify the structure and activity of chromatin. In addition, histone–DNA interactions in nucleosomes are modulated ('remodeled') to facilitate the interaction of factors with the DNA template (see, for example, Refs. 8–19).

In this review, we will discuss the function of chromatin-remodeling enzymes, which are ATP-dependent machines that modulate histone–DNA interactions in chromatin. These factors are involved in a wide range of processes, which include transcription, replication, repair, recombination and nucleosome assembly. We will describe chromatin-remodeling factors and their properties, and then present two distinct models by which different types of chromatin-remodeling factors may function to alter chromatin structure.

Activities of chromatin-remodeling factors

The term 'chromatin remodeling' generally refers to a discernable change in histone–DNA interactions in a nucleosome. There is a variety of assays by which chromatin remodeling has been investigated in vitro. Chromatin-remodeling factors have been observed to catalyze the mobilization and repositioning of nucleosomes, the transfer of a histone octamer

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Abbreviations: ACF, ATP-utilizing chromatin assembly and remodeling factor; ARIP4, androgen receptor interacting protein 4; BRG1, Brahma-related gene 1; BRM, Brahma; CHRAC, chromatin-accessibility complex; CSB, Cockayne Syndrome protein B; DDM1, decreased DNA methylation 1; ISWI, imitation switch; NoRC, nucleolar-remodeling complex; NURF, nucleosome-remodeling factor; RSC, remodels the structure of chromatin; RSF, nucleosome-remodeling and spacing factor; SWI/SNF, Switch/Sucrose non fermenting; TRF2, TBP-related factor 2; WCRF, Williams syndrome transcription factor-related chromatin-remodeling factor; WICH, WSTF-ISWI chromatin-remodeling complex.

from a nucleosome to a separate DNA template, the facilitated access of nucleases to nucleosomal DNA, the creation of dinucleosome-like structures from mononucleosomes, and the generation of superhelical torsion in DNA (reviewed for example in Refs. 8,12,14,19,20). These and other analyses provide important information on the mechanisms by which chromatin remodeling occurs. In addition to the alteration of histone–DNA contacts, chromatin-remodeling factors have been found to function in other chromatin-related processes. For instance, they can facilitate transcription from chromatin templates,[21–27] catalyze the assembly of periodic nucleosome arrays,[28–33] and participate in homologous strand pairing.[34,35]

Chromatin-remodeling factors—multiple machines with related motors

Chromatin-remodeling complexes are compositionally and functionally diverse, yet they share the presence of a motor subunit that belongs to the Snf2-like family of ATPases[36,37] (Fig. 1). Snf2-like family members can be further subdivided into several subfamilies according to the presence of protein motifs outside of the ATPase region.[37] For example, the SNF2 subfamily includes the yeast Swi2/Snf2 subunit of the SWI/SNF complex, the yeast Sth1 subunit of the RSC complex, and the *Drosophila* Brahma, human BRG-1, and hBRM subunits of SWI/SNF-related complexes in *Drosophila* and humans. SNF2 subfamily members contain a bromodomain in addition to the ATPase region. Other subfamilies and representative members (in parentheses) include ISWI (ISWI, hSNF2H, hSNF2L, yISW1, yISW2), CHD1 (CHD1, Mi-2α/CHD3, Mi-2β/CHD4, Hrp1, Hrp3), INO80, CSB (CSB, Rad26, ERCC6), RAD54 (Rad54, ATRX), and DDM1. Proteins from each of these subfamilies have been found to participate in ATP-dependent chromatin remodeling (Fig. 2).

The SWI/SNF complex, which contains the Swi2/Snf2 ATPase subunit in the SNF2 subfamily, is the most thoroughly studied chromatin-remodeling complex. It is a large (~2 MDa) complex that is conserved from yeast to humans. SWI/SNF complexes appear to be recruited to transcriptional regulatory regions by sequence-specific DNA-binding factors for the regulation of transcriptional activity via remodeling of chromatin structure.[16,38] In yeast, the SWI/SNF complex has been found to be involved in the regulation of about 5% of the genes.[39,40] The yeast RSC complex is closely related to the SWI/SNF complex in terms of its overall subunit composition and the similarity between Swi2/Snf2 and the Sth1 ATPase subunit of RSC.[41] From the biological standpoint, however, the RSC complex appears to have a more global effect on transcription than the SWI/SNF complex.[42–44]

There is a variety of chromatin-remodeling complexes that contain an ATPase subunit in the ISWI subfamily (also known as the SNF2L subfamily; Ref. 37). The *Drosophila* ISWI protein is a common subunit of the NURF, CHRAC and ACF complexes. In vertebrates, members of the ISWI subfamily are the ATPase subunits of the RSF complex,[23] hACF/WCRF complex,[29,45] xACF,[46] WICH complex,[47] hCHRAC[48] and NoRC.[49] In addition, ISW1 and ISW2 are the catalytic subunits of chromatin-remodeling complexes in yeast.[50–52] ISWI has also been observed to copurify with a *Drosophila* TRF2 complex.[53] Unlike SNF2 subfamily proteins, ISWI subfamily members lack a bromodomain and contain a SANT (SWI3, ADA2, N-CoR, TFIIIB) domain. ISWI-subfamily-based complexes tend to possess fewer subunits (~two to four subunits) relative to SNF2-subfamily-containing complexes (~12 subunits). Moreover, in biochemical assays, SNF2-subfamily complexes (such as SWI/SNF) tend to disrupt nucleosome structure, whereas ISWI-subfamily complexes (such as ACF/CHRAC or RSF) have been observed to assemble nucleosomes or to enhance the stability of chromatin structure.

The CHD1 subfamily of ATPases contains a chromodomain and a DNA-binding motif. These proteins have been found in chromatin-remodeling factors, such as the NuRD and Mi-2 complexes, that additionally possess a histone deacetylase (HDAC) subunit.[54–56] The presence of CHD1-subfamily and histone deacetylase subunits in the same complex suggests that these factors may use chromatin-remodeling activity to facilitate the deacetylation of histones or other DNA-associated proteins.

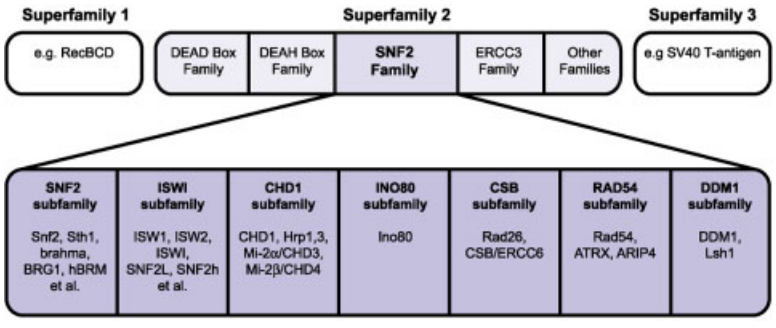

Figure 1. The SNF2-like family of ATPases includes many proteins that are involved in chromatin remodeling. This diagram depicts the classification of ATPases into three different superfamilies.[24] In superfamily 2, the SNF2-like family can be further divided into distinct subfamilies,[25] seven of which are listed here.

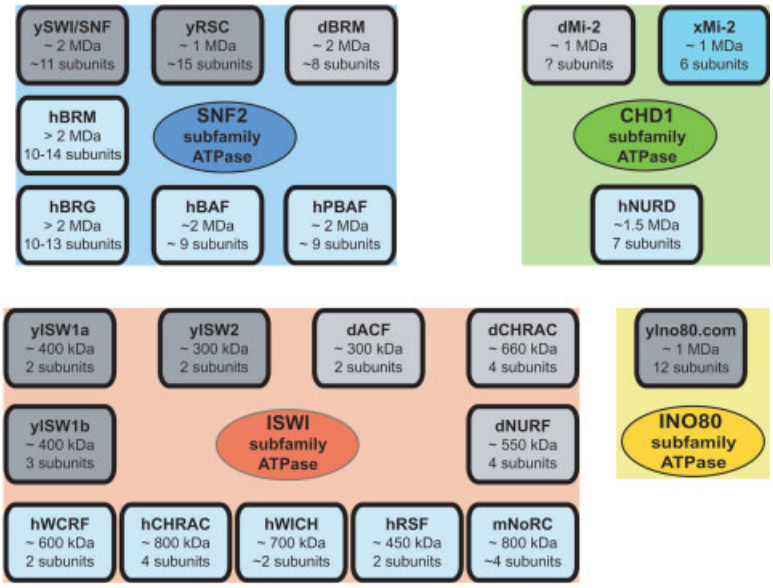

Figure 2. Members of the SNF2, ISWI, CHD1, and INO80 subfamilies are components of chromatin-remodeling complexes. Chromatin-remodeling complexes are symbolized by rectangles, and the approximate sizes and numbers of subunits are noted.

The Ino80 protein is in a large (~12 subunit) chromatin-remodeling complex termed Ino80.com.[57] In addition, Ino80.com contains the Rvb1 and Rvb2 proteins, which are related to the bacterial RuvB helicase that binds to Holliday junctions and promotes branch migration. Consistent with the presence of the Rvb1 and Rvb2 subunits, Ino80.com possesses DNA helicase activity. In fact, Ino80.com is the only chromatin-remodeling complex in which DNA helicase activity has been observed. It is possible that this helicase activity is due to the Rvb1 and/or Rvb2 subunits rather than the Ino80 protein. Mutation of the yeast INO80 gene results in sensitivity of yeast to hydroxyurea, methyl methanesulfonate, ultraviolet radiation and ionizing radiation. Moreover, Rvb1 and Rvb2 have been shown to directly or indirectly regulate the expression of about 5% of yeast genes.[58] These results suggest a role of Ino80.com in DNA repair as well as transcription.

Several other SNF2-like family proteins have been found to possess intrinsic ATP-dependent chromatin-remodeling activity. Rad54, which is involved in homologous recombination, functions cooperatively with Rad51 (which is related to bacterial RecA protein) in the remodeling of chromatin.[34,35,59] ARIP4 is an androgen receptor-interacting protein in the Rad54/ATRX subfamily that possesses chromatin-remodeling activity.[60] CSB (Cockayne Syndrome protein B) is a chromatin-remodeling protein that is involved in nucleotide excision repair.[61] Also, the plant DDM1 protein is a chromatin-remodeling factor that is important for the maintenance of DNA methylation and genome stability.[62,63] In the future, it will be interesting to determine whether Rad54, ARIP4, CSB and DDM1 naturally exist in multisubunit complexes.

Regulation of the ATPase motor subunits of the remodeling complexes

Individual ATPase subunits, such as BRG1, hBRM, Sth1, ISWI, SNF2H, and Mi-2, have been observed to mediate chromatin-remodeling activity, as measured in assays that monitor changes in histone–DNA interactions.[56,64–70] These findings indicate that the SNF2-like ATPase polypeptides possess an intrinsic chromatin-remodeling function.

What are the functions of the non-ATPase subunits of chromatin-remodeling complexes? First, the non-ATPase subunits may enhance or regulate the motor activity of the ATPase subunits. For instance, in the case of human SWI/SNF family complexes, chromatin remodeling by the BRG1 or hBRM ATPases is significantly stimulated by the INI1, BAF155 and BAF170 subunits of the complexes.[64] Second, the non-ATPase subunits can mediate other specialized functions that are unrelated to chromatin remodeling. For example, both the ATPase and non-ATPase subunits of SWI/SNF complexes have been found to be recruited to promoters via interactions with sequence-specific transcription factors (see, for example Refs. 21,24,27).

The *Drosophila* ISWI polypeptide is present in the NURF, ACF and CHRAC chromatin-remodeling complexes. In the NURF complex, the NURF301 subunit modifies the intrinsic nucleosome mobilization properties of the ISWI polypeptide.[71] In addition, NURF301 was found to interact with sequence-specific transcription factors.[71] In the ACF and CHRAC complexes, the Acf1 subunit stimulates the intrinsic chromatin assembly and remodeling activities of ISWI.[30,31,33,67,69] The Acf1 subunit also contains a DNA-

binding region that is important for the chromatin assembly activity of ACF.[30] Moreover, Acf1 affects the ability of ISWI to mobilize nucleosomes. ISWI alone will catalyze the movement of a nucleosome toward the ends of short (<400 bp) DNA fragments, whereas ACF (=Acf1 + ISWI) catalyzes the movement of nucleosomes toward the center of the same DNA fragments.[67,69] Thus, the specialized biochemical properties of the NURF and ACF/CHRAC complexes are determined by their respective NURF301 and Acf1 subunits.

Rad54 provides another example in which a SNF2-like ATPase is programmed by another polypeptide. Rad54 and Rad51 (which is related to bacterial RecA protein) have been observed to catalyze homologous strand pairing in vitro with naked DNA templates. In chromatin-remodeling assays, Rad54 has a low intrinsic activity that is strongly enhanced by the addition of Rad51 protein.[34,35,59] In addition, Rad54 and Rad51, but not bacterial RecA protein, are able to catalyze homologous strand pairing with chromatin templates.[34,35] In fact, in the absence of superhelical torsion, strand pairing by Rad54 and Rad51 is greater than 100 times more efficient with chromatin templates than with non-chromatin templates.[34] It thus appears that Rad54 and Rad51 have evolved to function optimally with chromatin rather than naked DNA templates. These studies of Rad54 and Rad51 indicate that Rad51 regulates the chromatin-remodeling activity of Rad54 and functions with Rad54 to catalyze the homologous-strand-pairing reaction in chromatin.

Hence, these findings provide examples in which the activities of the SNF2-like ATPase motor proteins can be programmed by other proteins. Moreover, one potential mechanism for the regulation of the ATPases has been suggested in the analysis of the dMi-2 ATPase subunit of the *Drosophila* Mi-2 complex. Deletion of specific subregions of Mi-2 was found to result in a moderate increase in its ATPase and nucleosome-sliding activities.[72] It is thus possible that there is some negative autoregulation of the Mi-2 protein that is relieved by the binding of other polypeptides.

How might chromatin remodeling occur?

There has been considerable effort devoted toward the analysis of the mechanisms of chromatin remodeling (for reviews, see Refs. 8,9,12,14,15,19,20,73). In this section, we will speculate on some of the possible features of the chromatin-remodeling process.

Chromatin-remodeling factors exhibit a variety of biochemical activities, some of which are as follows. (1) Nuclease I digestion assays have revealed that SNF2 subfamily complexes disrupt histone–DNA contacts in mononucleosomes,[41,74,75,76] whereas this disruption of histone–DNA contacts was not seen in analogous experiments with ISWI subfamily members.[68,69] (2) Chromatin-remodeling factors can catalyze mobilization (which is sometimes termed 'sliding') of nucleosomes relative to the DNA template.[52,59,63,69,71,77–83] (3) SNF2 subfamily complexes, but not ISWI subfamily complexes, can mediate the transfer of histones from one DNA template to a separate DNA template.[69,80,84,85] (4) SNF2 subfamily complexes catalyze the apparent disassembly of nucleosomes, as assessed by the loss of DNA supercoiling of chromatin templates.[68,75,81,82,86–89] [Note that the wrapping of DNA around a core histone octamer results in a change in the linking number of approximately −1. The loss of negative DNA supercoils in circular nucleosomal DNA (in the presence of topoisomerase I to relieve superhelical torsion) thus indicates the loss of canonical nucleosomes.] In contrast, ISWI subfamily members, such as ACF, CHRAC, and RSF, promote the assembly of nucleosomes.[28–30,32,33,51] (5) SNF2 subfamily complexes, but not ISWI subfamily members, have also been observed to form dinucleosome-size structures from mononucleosomes.[69,82,85,88,90] (6) A variety of remodeling factors have been observed to generate superhelical torsion in DNA or chromatin.[35,60,91] (7) RSC complex, ISWI and Rad54 have been found to exhibit triplex DNA displacement activity and thus appear to translocate along the DNA.[65,92] [In the triplex DNA displacement assay, a short oligonucleotide that binds in the major groove of a pyrimidine-rich target sequence is displaced by motor proteins that translocate through the sequence.] Furthermore, the ACF complex exhibits template commitment during chromatin assembly, which suggests that it functions as a DNA-translocating enzyme.[31] These and other data collectively suggest that the SNF2 subfamily complexes generally appear to disrupt chromatin structure, whereas ISWI subfamily complexes tend to yield stable chromatin structures.

The contrast between SNF2 versus ISWI subfamily factors has been further illuminated by photocrosslinking experiments.[78,83] These studies involved the use of a mutant version of histone H4 in which serine residue 47 was modified to cysteine to allow the covalent attachment of a photoreactive aryl azide moiety. Mononucleosomes were then reconstituted with the S47C mutant H4, and their positions were mapped by photocrosslinking of the modified cysteine residue to the DNA. By using this assay, the yeast ISW2 complex (which appears to be related to the metazoan ACF and CHRAC complexes) was observed to catalyze a modest repositioning of nucleosomes by about 10 bp.[78] In sharp contrast, the yeast SWI/SNF complex was found to mediate the translocation of nucleosomes by about 50 to 80 bp.[83] Moreover, with a 183 bp DNA fragment, SWI/SNF remodeling results in the movement of the histone octamer off the end of the DNA such that only about 95 bp of DNA remain associated with the octamer. These findings provide new insight into the differences between chromatin remodeling by ISWI and SNF2 family complexes. A summary of the activities of these complexes is shown in Fig. 3.

Potential mechanisms for chromatin remodeling have been tested and discussed extensively (see, for instance:

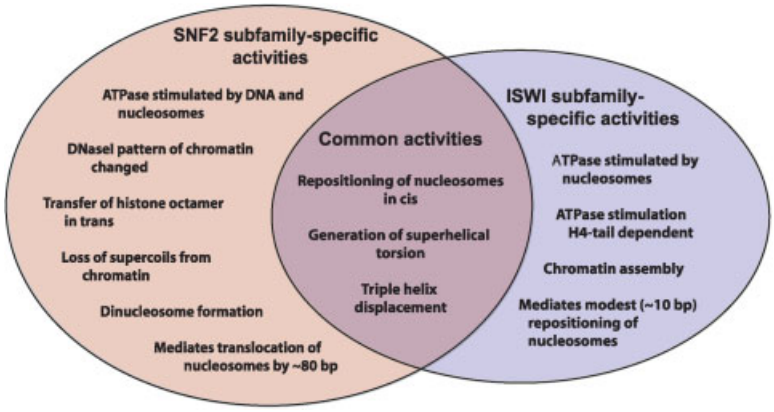

Figure 3. A summary of the activities of SNF2 and ISWI subfamily complexes.

Refs. 8,15,20,31,35,65,68,77,78,82,83,85,91–94). Most of the proposed mechanisms involve the generation of a DNA loop or bulge (of variable size) that is propagated across the surface of the histone octamer. In one model, such as that depicted in Fig. 4, the DNA loop is generated by ATP-driven translocation of the remodeling factor. In another model, a short loop of DNA dissociates from the histone octamer as the DNA is twisted by the chromatin-remodeling factor. It has also been proposed that thermal energy alone is responsible for the initial dissociation of DNA from the ends of the nucleosome.[95] Another version of this looping model suggests that the remodeling factor pushes the DNA toward the histone octamer.

At present, the available data are generally consistent with all of these proposed models for chromatin remodeling. We would, however, like to offer some of the following speculations. First, given the significant differences in the biochemical activities of ISWI and SNF2 subfamily complexes, it is probably best to consider distinct mechanisms of action for the SNF2 and ISWI subfamily complexes. Hence, the results obtained with SNF2 subfamily complexes may not be relevant to the analysis of ISWI subfamily complexes, and vice versa. Second, most biological processes are actively controlled by enzymes—even the hydration of carbon dioxide into carbonic acid is catalyzed by an enzyme. Thus, we prefer models in which the remodeling enzyme is actively involved in chromatin remodeling throughout the entire process. In the remainder of this review, we will briefly discuss possible models for chromatin remodeling by ISWI and SNF2 subfamily complexes.

Two possible models for chromatin remodeling by molecular machines

With the ISWI subfamily complexes, we favor the ATP-driven DNA translocation model, which is depicted in Fig. 4. This model is supported by the ability of ACF and ISWI to

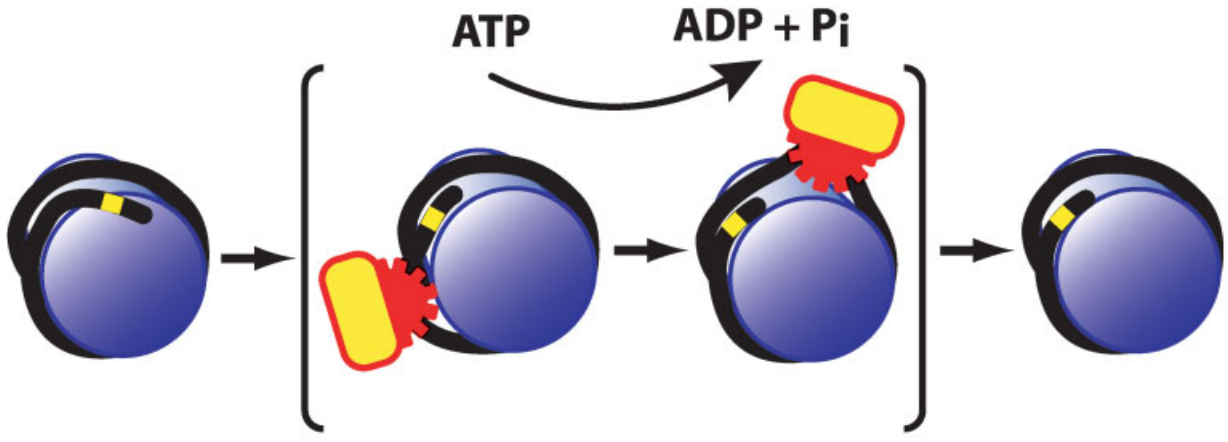

Figure 4. A DNA translocation model for nucleosome remodeling by ISWI subfamily complexes. In this model, an ISWI subfamily complex is an ATP-driven DNA-translocating enzyme that disrupts contacts between histones and DNA. After passage of the enzyme, histone–DNA contacts are reestablished to give a canonical nucleosome that is located at a different position relative to the DNA template.

translocate along DNA[31,92] as well as the general propensity of ISWI subfamily complexes to assemble nucleosomes rather than to disassemble nucleosomes.[28,29,32,33,51] This model (with a small loop) is also consistent with the inability of ISWI subfamily complexes to catalyze the transfer of histones from one template to another template or to form dinucleosome-like structures from mononucleosomes, although such activities have been observed with SNF2 subfamily complexes.[69,80,82,84,85,88,89,90] In addition, nucleosomes containing nicked DNA can be efficiently remodeled by ISWI and even be a better substrate than intact DNA when the nicks are positioned at the edge of the nucleosome.[77] These results argue against a requirement for torsional stress in chromatin remodeling. Lastly, the DNA-translocation model involves the active control of remodeling throughout the entire process, which is an aesthetically pleasing feature in an enzymatic mechanism.

For the SNF2 subfamily complexes, we suggest a lateral cross-transfer mechanism, as shown in Fig. 5. In this model, the nucleosomal DNA undergoes a lateral cross-transfer that moves one superhelical turn of DNA to the adjacent track and dissociates the other superhelical turn of DNA from the histone octamer. This cross-transfer might result in a net DNA translocation relative to the octamer of about 80 bp, which is consistent with the results obtained in the photocrosslinking analysis of the yeast SWI/SNF complex.[83] This model is also in accord with the general tendency of SNF2 subfamily factors to disrupt nucleosomes.[68,75,76,81,82,86,88,89,96] In addition, the reaction product (Fig. 5, right panel) could form dinucleosome structures, as seen with SNF2 subfamily complexes but not with ISWI complexes,[69,82,85,88,90] by *trans*-attachment of the long DNA overhang of one remodeled nucleosome with the histone octamer of another remodeled nucleosome. Moreover, the dissociation of a significant proportion of the nucleosomal DNA would promote transfer of the histones from one DNA fragment to a separate DNA template, as mediated by SNF subfamily complexes but not ISWI subfamily complexes.[69,80,84,85] We will not speculate further on the specific details by which the lateral cross-transfer might occur, but rather suggest that this model could be further tested and either supported or disproven.

Conclusions

Chromatin-remodeling complexes are ATP-dependent molecular motors that modulate nucleosome structure. Chromatin-remodeling factors share an ATPase subunit that is a member of the SNF2-like family of proteins, and they function in a broad range of biological processes that include transcriptional regulation, DNA repair, homologous recombination and chromatin assembly. The molecular mechanisms of chromatin remodeling remain to be determined. Although remodeling factors possess related ATPase subunits, the available data suggest that these enzymes may not act by a single common mechanism.

Some questions for the future are as follows. First, how many other chromatin-remodeling factors remain to be identified? There are other subfamilies of the SNF2-like family that have not yet been tested for chromatin-remodeling activity, and it is also possible that ATPases in other related families are involved in the remodeling of chromatin. Second, what is the range of biological processes that involve the ATP-dependent remodeling of chromatin? Any phenomenon that involves DNA

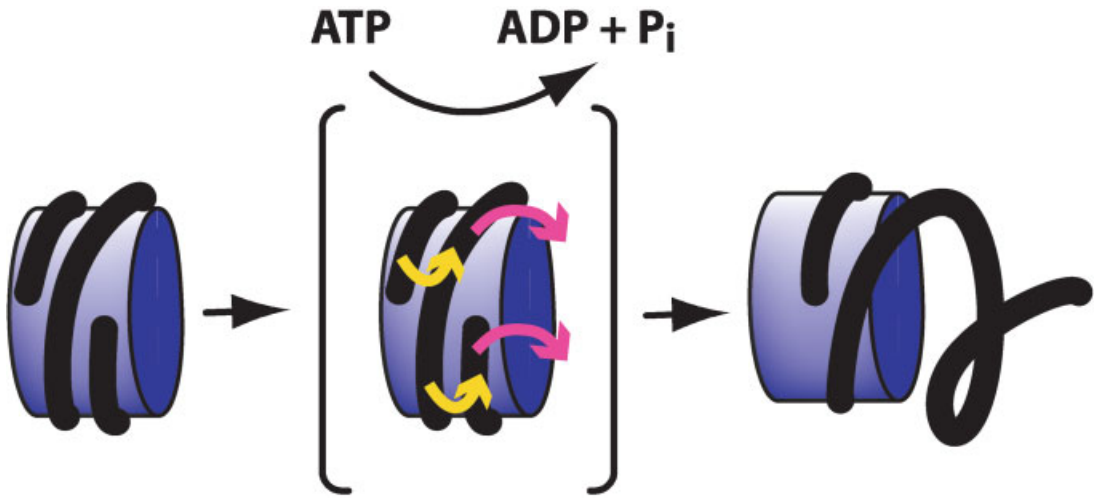

Figure 5. A lateral cross-transfer model for nucleosome remodeling by SNF2 subfamily complexes. In this model, a SNF2 subfamily complex catalyzes the rearrangement of one superhelical turn of nucleosomal DNA to the adjacent track on the histone octamer while the other superhelical turn of DNA is displaced from the nucleosome.

or chromosomes in the eukaryotic nucleus is potentially dependent upon chromatin-remodeling activity. Third, how do chromatin-remodeling factors work? It will be particularly important to study these factors in the context of their natural biological functions. Fourth, what are the mechanisms by which chromatin-remodeling activity is regulated? There are many interesting and important features of these ATP-dependent molecular machines that remain to be discovered.

Acknowledgments

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