Cell, Vol. 88, 737–740, March 21, 1997, Copyright ©1997 by Cell Press

SWI2/SNF2 and Related Proteins: ATP-Driven Motors That Disrupt Protein–DNA Interactions?

Minireview

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A central question in the analysis of transcription factors in eukaryotes is how these DNA-binding proteins function with a chromatin template. The binding of factors to chromatin templates occurs readily in vivo as well as in vitro in the presence of factors in crude chromatin assembly extracts. Yet, on the other hand, biochemical experiments with purified or partially purified nucleosomal templates indicate that the packaging of DNA into chromatin is often, but not always, an impediment to the binding of proteins to DNA. It is therefore reasonable to consider that there may be specialized factors that can act to facilitate the function of DNA-binding proteins with chromatin. In this regard, recent work from a number of laboratories has led to the postulate that SWI2/SNF2 and related proteins can function to destabilize nucleosome structure and thereby to facilitate the binding of transcription factors to chromatin (reviewed in Winston and Carlson, 1992; Eisen et al., 1995; Peterson and Tamkun, 1995; Kingston et al., 1996). In this minireview, we will briefly summarize some recent findings in this area.

The SWI/SNF Complex

Genetic studies of transcriptional regulation in Saccharomyces cerevisiae led to the identification of a number of *SWI* and *SNF* genes (SWI refers to yeast mating type *switching*, while *SNF* is an abbreviation for *sucrose nonfermenting*; some of these genes were also found in other contexts). These genes did not appear to encode sequence-specific DNA-binding proteins but were required to achieve the proper amount of transcription from a limited number of promoters. One of the *SWI* genes, *SWI2*, was found to be identical to one of the *SNF* genes, *SNF2*, and hence, this gene is referred to as *SWI2/SNF2*. Further experiments revealed a functional interdependence among some of the SWI and SNF proteins—specifically, SWI1, SWI2/SNF2, SWI3, SNF5, and SNF6—which hinted that they may act together as a complex. In addition, a relation between SWI/SNF protein function and chromatin structure was suggested by two key observations. First, many of the suppressors of defective SWI/SNF function in S. cerevisiae were found to be genes that encode components of chromatin, such as the core histones. Second, in the *SUC2* gene, the absence of either SWI2/SNF2 or SNF5 results in a decrease in transcription and an alteration of the chromatin structure in the promoter region, and both of these effects can be suppressed by a reduction in the level of the core histones H2A and H2B.

Biochemical studies of SWI/SNF proteins led to the purification of an ~2 MDa protein complex, which is commonly known as the SWI/SNF complex, from yeast and mammalian cells (note that many of the yeast and mammalian components of the complex appear to be homologous; Wang et al., 1996). As predicted from the genetic data, the SWI/SNF complex contains SWI1, SWI2/SNF2, SWI3, SNF5, and SNF6 proteins in addition to several other polypeptides. The ability of the SWI/SNF complex to affect chromatin structure was then tested. These experiments revealed that the SWI/SNF complex possesses a DNA-stimulated ATPase activity and can destabilize histone-DNA interactions in reconstituted nucleosomes in an ATP-dependent manner, though the exact nature of this structural change is not known. In addition, this SWI2/SNF2-mediated destabilization of nucleosomes was found to increase the binding of transcription factors, such as GAL4 derivatives or the TATA box-binding protein (TBP), to the histone-associated DNA. These results, combined with the genetic data, led to the hypothesis that the SWI/SNF complex facilitates the binding of transcription factors to chromatin.

SWI2/SNF2 Is a Member of a Large Group of Related Proteins

The SWI2/SNF2 polypeptide contains the characteristic seven conserved protein motifs that are present in a large and rapidly growing group of nucleoside triphosphate (NTP)-binding proteins that include DNA and RNA helicases (reviewed in Gorbalenya and Koonin, 1993; Eisen et al., 1995). Comparative amino acid sequence analysis revealed that this group of helicases and related proteins comprises at least three superfamilies, which in turn can be further divided into families and subfamilies (reviewed in Gorbalenya and Koonin, 1993; Eisen et al., 1995). The conserved structure of these proteins may reflect a similar mechanism of action (Travers, 1992; Eisen et al., 1995). For instance, both E. coli recBCD and SV40 large T antigen, which are DNA helicases, can disrupt chromatin structure in vitro. As illustrated in Figure 1, SWI2/SNF2 is in the SNF2 subfamily of the SNF2-like family of the SF2 superfamily. (Unfortunately, from the standpoint of nomenclature, there is both a SNF2 subfamily and a SNF2-like family.) Mutagenesis of the conserved NTP-binding motif in SWI2/SNF2 results in a significant reduction in ATPase activity and facilitated transcription factor binding to mononucleosomes, as mediated by the SWI/SNF complex (Côté et al., 1994). Hence, the conserved helicase-like motif in SWI2/SNF2 appears to be an important component of the activity of the SWI/SNF complex as seen in the biochemical assays.

Interestingly, members of the SNF2-like family exhibit an impressive range of biological functions. These activities include gene-specific transcriptional activation (SNF2 subfamily), transcriptional repression (MOT1), destabilization of reconstituted nucleosomes (SNF2 and SNF2L subfamilies), transcription-coupled repair (ERCC6 subfamily), nucleotide excision repair of nontranscribed regions of the genome (RAD16), recombination repair (RAD54 subfamily), and chromosome segregation (lodestar). In spite of the presence of the

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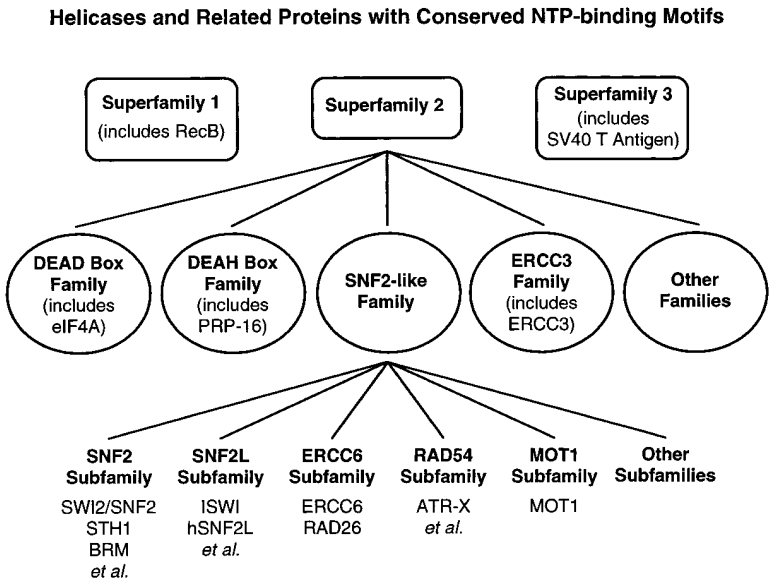

Figure 1. The SNF2-like Family of Proteins Contains Conserved NTP-Binding Motifs That Are Also Present in DNA and RNA Helicases

This diagram is adapted from the analysis and nomenclature of Gorbalenya and Koonin (1993) and Eisen et al. (1995). Selected examples of families and proteins are shown, and a more complete list is available from those references.

conserved helicase-like motif in these proteins, however, helicase activity has not yet been detected in any SNF2-like family member.

SNF2-like family members are also involved in human disease. Mutations in the human *ERCC6* gene can lead to Cockayne's syndrome, which is characterized by progressive neurodegeneration, dwarfism, photosensitivity, and developmental abnormalities (Troelstra et al., 1992). In addition, mutated forms of the human *ATR-X* gene (also known as *NUCPRO*; tentatively assigned to the *RAD54* subfamily) cause a combined α-thalassemia and mental retardation syndrome (Gibbons et al., 1995).

RSC—A SWI/SNF-like Complex That Contains STH1, a Member of the SNF2 Subfamily

A SWI/SNF-like complex termed RSC (remodel the structure of chromatin) has been recently purified and characterized from S. cerevisiae (Cairns et al., 1996). RSC is an $\sim$1 MDa complex that contains an estimated 15 polypeptides, at least three of which are related to components of the SWI/SNF complex: STH1 (related to SWI2/SNF2); RSC6 (related to SWP73); and RSC8 (related to SWI3). Like the SWI/SNF complex, RSC has a DNA-stimulated ATPase activity and is able to alter histone-DNA interactions in reconstituted mononucleosomes in an ATP-dependent manner, but the nature of this structural change is not known. The STH1 (SNF two homolog) subunit of RSC has been categorized as a member of the SNF2 subfamily (Eisen et al., 1995) (see Figure 1), and this close similarity of STH1 to SWI2/SNF2 is consistent with the related biochemical activities of the SWI/SNF complex and RSC. Unlike the constituents of the SWI/SNF complex (which are encoded by nonessential genes), STH1, RSC6, and RSC8 are encoded by genes that are essential for mitotic growth in S. cerevisiae (Laurent et al., 1992; Cairns et al., 1996). Moreover, a LexA-STH1 fusion protein does not appear to activate transcription under conditions where an analogous LexA–SWI2/SNF2 protein functions as a transcriptional activator (Laurent et al., 1992). At present, downstream targets of RSC function have not yet been identified. Thus, while it seems likely that RSC is involved in some aspect of the transcription process, it may be worthwhile to consider other possible functions for this protein complex, such as DNA replication or chromosome organization.

NURF—A Complex Containing ISWI, a Member of the SNF2L Subfamily

The analysis of an ATP-dependent activity that is required to alter nucleosome structure upon binding of the GAGA transcription factor (a sequence-specific DNA-binding factor in Drosophila) has led to the purification of a factor termed NURF (nucleosome remodeling factor) from Drosophila embryos (Tsukiyama and Wu, 1995). NURF is an $\sim$0.5 MDa complex that contains four polypeptides, one of which is the ISWI (imitation switch) protein. ISWI is a member of the SNF2L subfamily, which is closely related to the SNF2 subfamily (Figure 1). At present, downstream targets of ISWI are not known. The biochemical activities of NURF are similar but not identical to those of SWI/SNF complex or of RSC. For instance, all three complexes can stimulate the binding of transcription factors to reconstituted mononucleosomes in an ATP-dependent manner. On the other hand, the ATPase activity of RSC or SWI/SNF complex is stimulated by free DNA or by nucleosomes, while the ATPase activity of NURF is stimulated by nucleosomes, but not by free DNA. It seems likely, given the available evidence, that ISWI will be the key ATP-utilizing component of NURF.

MOT1, a Member of the SNF2-like Family, Can Dissociate TATA Box-Binding Protein (TBP) from DNA by an ATP-Dependent Process

Studies of MOT1 (modifier of transcription; also known as ADI, for ATP-dependent inhibitor of TBP binding), another member of the SNF2-like family of proteins (Figure 1), may provide some insight into the function of SWI2/SNF2, STH1, and ISWI proteins. MOT1 was identified both genetically and biochemically as a repressor of basal transcription (Auble et al., 1994, and references therein). The biochemical experiments revealed that

MOT1 specifically recognizes TBP and can dissociate TBP from TBP-DNA complexes by an ATP-dependent process. In addition, mutational analysis of MOT1 indicated that its conserved NTP-binding motif was required to observe ATPase activity and dissociation of TBP-DNA complexes in vitro as well as to complement the phenotype of the mutant *mot1-1* allele in vivo. These and other data indicate that MOT1 can repress basal transcription by specific recognition of TBP and dissociation of TBP-DNA complexes by an ATP-dependent mechanism.

SNF2-like Family Members: ATP-Driven, DNA-Translocating Enzymes That Remove Proteins from DNA?

The available data on SWI/SNF complex (SWI2/SNF2), RSC (STH1), NURF (ISWI), and MOT1 suggest, as proposed earlier (Auble et al., 1994; Eisen et al., 1995; and others), that these factors may function as ATP-driven motors that translocate along DNA and destabilize protein-DNA interactions. The movement of these proteins along DNA is likely to be similar to the ATP-dependent translocation of helicases along nucleic acids, given the conserved NTP-binding motif in these factors. How might such an activity be envisaged to function with nucleosomal templates? In this regard, it might be useful to consider the "spooling" mechanism that has been suggested for the procession of polymerases—which are also NTP-driven DNA-translocating motors—through nucleosomes (Kornberg and Lorch, 1995; Studitsky et al., 1995; and references therein). In this model, a DNA-translocating protein uses the energy derived from hydrolysis of ATP to traverse a nucleosome in a wave-like manner that results in only a partial disruption of the nucleosome at any particular point (Figure 2). This sort of process could account for the ATP-dependent destabilization of nucleosome structure and facilitated transcription factor binding that has been observed in vitro with SWI/SNF complex, RSC, or NURF. (Where examined, the ATP-dependent SWI/SNF-mediated changes in histone-DNA interactions in nucleosomes have been shown to persist after removal of ATP; in such cases, it seems possible that the histones and DNA remain associated in a nonnucleosomal state in which transcription factors have facilitated access to the DNA.) Also, as depicted in Figure 2, the translocation of these proteins could facilitate changes in nucleosome positioning, as seen with nucleosome arrays in vitro (see, for example: Pazin et al., 1994; Tsukiyama and Wu, 1995; Varga-Weisz et al., 1995). With MOT1, the specificity of the factor for TBP would likely be achieved by direct binding of MOT1 and TBP, and then dissociation of TBP could be mediated by an analogous DNA translocation mechanism. Thus, this ATP-driven DNA translocation mechanism seems to be consistent with the available data on the properties of the SNF2-like family members.

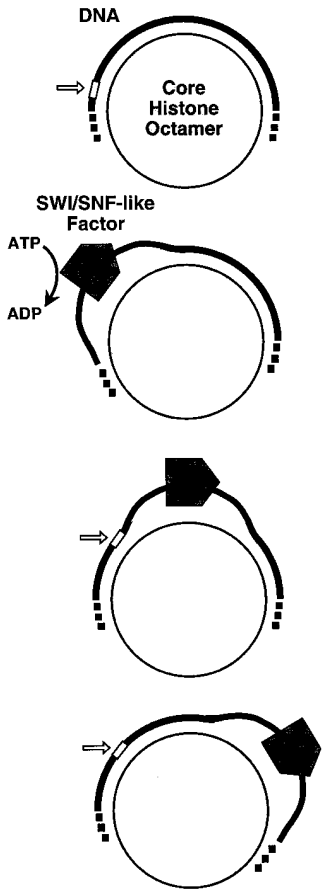

Figure 2. A Simple Model Depicting a Suggested Mechanism for the Destabilization of Nucleosomes by SWI/SNF Complex and Related Factors by ATP-Driven Translocation of the Protein along Nucleosomal DNA

This model is similar to the spooling mechanism described by Studitsky et al. (1995) for the passage of polymerases through nucleosomes. There may be positive DNA supercoiling generated in "front" (i.e., the direction of travel) of the enzyme and negative supercoiling "behind" the enzyme during procession of the protein through the nucleosome, and as noted by Travers (1992), Studitsky et al. (1995), and others, this positive and negative supercoiling would likely affect the stability of the histone-DNA interactions. As denoted by the open arrows and rectangular boxes (the open rectangular box represents a specific position in the DNA), the wave-like procession of the enzyme across the nucleosome would probably result in a change in the position of the DNA relative to the histone octamer. While this figure depicts the reassembly of the proper histone-DNA contacts of the nucleosome after passage of the protein complex, it is possible that some forms of nucleosome "disruption" or "remodeling" involve a nonnucleosomal state wherein the histone-DNA contacts remain altered after translocation of the factor.

Some Other Questions and Issues

For further thought, we have included some additional questions. There has been a significant body of new data on SWI/SNF and related complexes, and there are many interesting and important issues that will likely be clarified in the near future.

Is the specificity in the function of the SWI/SNF complex due to targeting of the complex to the appropriate genes (such as through interactions with DNA-bound transcription factors [direct mechanism]), or does the SWI/SNF complex globally facilitate nucleosome mobility in a manner that affects the transcriptional state of only a subset of genes that are sensitive to such changes in chromatin structure (indirect mechanism)?

SWI/SNF complex, RSC, and NURF appear to comprise about 4 to 15 polypeptides. What is the function of the polypeptides in SWI/SNF and related complexes that do not possess the conserved NTP-binding motif?

For example, are some of the other subunits involved in regulation of the activity of the complex, interactions with other transcription factors, or subcellular localization?

Is the SWI/SNF complex an integral component of the RNA polymerase II holoenzyme? There are conflicting data regarding this point (Cairns et al., 1996; Wilson et al., 1996).

It has been shown that SWI/SNF complex can facilitate the nucleosome-inhibited binding of GAL4 derivatives to DNA in a mononucleosome. Analogously, NURF can facilitate the nucleosome-inhibited binding of the GAGA factor to DNA in a mononucleosome. In contrast, however, the binding of GAL4 derivatives, GAGA factor, and NF-E2 do not appear to be inhibited by packaging of DNA into extended nucleosome arrays (as opposed to mononucleosomes), even in the absence of ATP-dependent SWI/SNF-like activities (Pazin et al., 1994; Tsukiyama and Wu, 1995; Armstrong and Emerson, 1996). What is the basis for this apparent difference? Are internucleosomal interactions important for the proper functioning of transcription factors?

Do transcriptional activation domains participate in the SWI/SNF complex-facilitated binding of factors to chromatin? Studies from different laboratories have led to different conclusions regarding this point. It appears, however, that activation domains can increase the binding of factors to chromatin in vivo. In those instances, is the activation domain directly involved in the binding of the factor to the nucleosome (i.e., does it interact directly with the core histones and/or the DNA), or is it required for cooperative binding with another transcription factor?

Lastly, what happens to the nucleosomes upon addition of SWI/SNF complex (or RSC or NURF) and ATP? This process is often referred to as “remodeling.” Is remodeling the dissociation of some or all of the core histones from DNA, is it a conformational change, or is it some other alteration/modification of the nucleosome?

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