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The "Dark Side" of Chromatin Remodeling: Repressive Effects on Transcription

Minireview

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The packaging of the eukaryotic genome into chromatin permits dynamic and broad-ranging changes in gene expression. The basic unit of chromatin is the nucleosome, which comprises ~200 bp of DNA wrapped about two turns around an octamer of core histone proteins (Luger et al., 1997; reviewed by Kornberg and Lorch, 1999). The assembly of a gene into chromatin generally represses transcription by inhibiting the binding and function of key components of the transcriptional apparatus. To facilitate the function of such factors in the context of chromatin, there are a variety of ATP-utilizing chromatin remodeling factors whose fundamental function is the mobilization of nucleosomes via the alteration of histone–DNA contacts.

Chromatin remodeling complexes have been generally studied as factors that promote gene activation (recently reviewed by Travers, 1999; Varga-Weisz and Becker, 1999). In this minireview, we will first provide a brief overview of chromatin remodeling. Then, we will turn toward the dark (i.e., repressive) side of these chromatin remodeling factors and describe recent studies indicating that ATP-driven chromatin remodeling factors facilitate not only transcriptional activation, but also repression. Lastly, we will compare the processes of chromatin remodeling and nucleosome assembly. Notably, these two related processes are both essential for the proper regulation of gene expression.

A Growing Family of ATP-Utilizing Chromatin Remodeling Factors

Chromatin remodeling factors comprise an ATPase subunit along with other polypeptides that are responsible for the regulation, efficiency, and functional specificity of each complex (Table 1). The ATPase subunits are members of a superfamily of proteins that contain a conserved NTP-binding motif (for a comparative sequence analysis, see: http://www.stanford.edu/~jeisen/SNF2/snf2.html). As shown in Table 1, the currently known chromatin remodeling factors possess ATPase subunits that are in the SWI2/SNF2 family (also known as the SNF2 subfamily), the Mi-2/CHD family (also known as the CHD1 subfamily), or the ISWI family (also known as the SNF2L subfamily). Moreover, there are many other proteins in sequence databases that are closely related to the ATPase subunits of chromatin remodeling complexes. It thus seems likely that there are many chromatin remodeling complexes that remain to be discovered.

How Do Remodeling Factors Mobilize Nucleosomes?

Chromatin remodeling factors use the energy derived from ATP hydrolysis to catalyze nucleosome mobilization, which is a net change in the position of the histone octamer relative to the DNA. The movement of a histone octamer along the DNA must involve the breaking and reestablishment of histone–DNA contacts within the nucleosome, but exactly how the histone–DNA contacts are altered is not known. In theory, the ATP-driven translocation of a chromatin remodeling complex along the DNA could directly break the histone–DNA contacts within a nucleosome. Alternatively, remodeling complexes may function in an indirect manner to alter histone–DNA contacts, such as by the induction of a general conformational change in the DNA and/or the histone octamer.

How the histone octamers move relative to the DNA is a matter of conjecture, and several different models have been proposed (for animations, see: http://www.dundee.ac.uk/~taowenhu/Toh_show.htm). Most of these current models have, however, a related theme of octamer movement, which is as follows. First, DNA dissociates from the histone octamer at one edge of the nucleosome. Then, a neighboring stretch of DNA associates with the histone octamer (to reestablish the previously

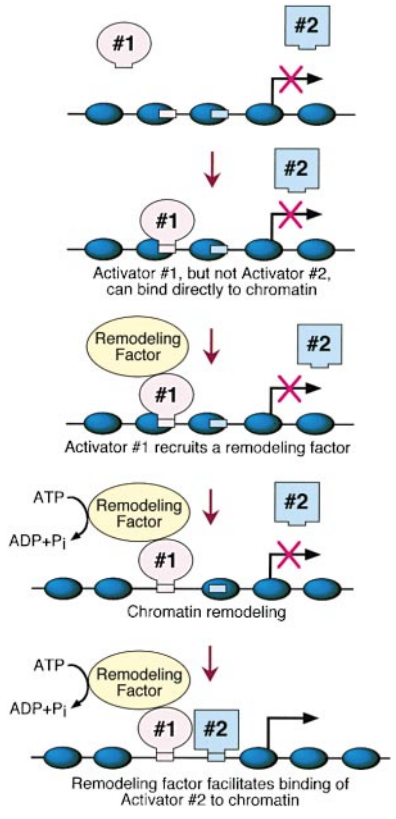

Figure 1. A Model for the Role of Chromatin Remodeling Complexes in the Binding of Transcription Factors to Chromatin

In this scheme, factors that can bind directly to DNA packaged into chromatin, as represented by Activator #1, facilitate the binding of factors that cannot bind to chromatin, as represented by Activator #2, via the recruitment of a chromatin remodeling factor by Activator #1.

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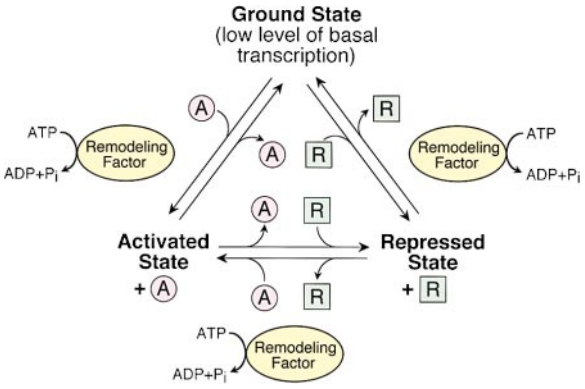

Figure 2. The Mobilization of Nucleosomes by Chromatin Remodeling Factors Facilitates Transcriptional Activation and Repression

In this model, the hypothetical "ground state" refers to the gene in the absence of sequence-specific DNA-binding activators or repressors. The "activated state" or "repressed state" of the gene is achieved upon binding of transcriptional activators ("A") or repressors ("R") to chromatin, as facilitated by chromatin remodeling factors. It should be noted, however, that both transcriptionally active and inactive genes are typically observed to be bound by various sequence-specific DNA-binding factors in vivo. Hence, it seems likely that most genes exist in either an activated state or a repressed state.

broken histone–DNA contacts) to yield a DNA loop that is propagated in a wave-like fashion across the surface of the octamer. (Note: some models differ in the size of this loop, which could be as small as 1 bp, and whether or not the DNA turns on its lengthwise axis as the loop is being propagated.) A key feature of this general hypothesis is that only a small stretch of histone–DNA contacts is broken at any given time, as histone–DNA contacts are being formed at the same time that they are being disrupted. Moreover, the *trans*-displacement of an octamer from one DNA molecule to another could also occur by a similar mechanism, wherein histone–DNA contacts are broken with one DNA molecule and then re-formed with a different DNA molecule.

In addition to catalyzing nucleosome mobility, chromatin remodeling factors can enhance the access of DNA-binding factors and nucleases to DNA packaged into chromatin. These activities are also consistent with the ability of remodeling factors to disrupt histone–DNA interactions in the nucleosome.

Who Recruits Whom?

Some nucleosome remodeling factors, such as SWI/SNF complex, appear to be targeted to specific regions of the genome. This topic of targeted nucleosome remodeling raises the "chicken and egg"–like question of who recruits whom? Does the DNA-binding factor recruit the remodeling complex to the DNA? Or, does the remodeling complex facilitate access of the DNA-binding protein to the DNA? In fact, both scenarios are likely to be correct. Some activators, such as glucocorticoid receptor and Gal4-VP16, can bind with high affinity to DNA packaged into chromatin, whereas other factors, such as CTF/NF-I, cannot bind to their recognition sites in chromatin. Thus, as depicted in Figure 1, activators that can bind to DNA in chromatin could recruit a remodeling complex to the promoter that, in turn, facilitates the binding of other factors that cannot bind directly to chromatin. Consistent with this idea, glucocorticoid receptor and Gal4-VP16 have each been shown to bind to the SWI/SNF complex (Neely et al., 1999 and references therein). In addition, this model for facilitated factor access is supported by recent experimental analyses

Table 1. ATP-Utilizing Chromatin Remodeling Factors

Factor	ATPase	ATPase Essential?	Organism	No. of Subunits	Comments
SWI/SNF family					
SWI/SNF	SWI2/SNF2	no	*S. cerevisiae*	11	Required for activation and repression of specific genes.
RSC	STH1	yes	*S. cerevisiae*	15	Shares subunit similarities with SWI/SNF complex.
Brahma	BRM	yes	*D. melanogaster*	≥7	*Drosophila* counterpart of yeast SWI/SNF.
hSWI/SNF	hBRM	no	*H. sapiens*	~10	hSNF5/INI1 is associated with malignant rhabdoid tumors.
hSWI/SNF	BRG1	yes	*H. sapiens*	~10	Have tissue-specific subunit heterogeneity.
Mi-2/CHD family					
Mi-2 complex	Mi-2/CHD	yes	*X. laevis*	6	NuRD, NRD, NURD, and Mi-2 complex are related or identical.
NuRD	Mi-2/CHD	(in *Drosophila*)	*H. sapiens*	≥7	Complexes contain Mi-2α/CHD3 and/or Mi-2β/CHD4. Mi-2 subunit is a dermatomyositis-specific autoantigen. MTA2 subunit is related to metastasis-associated factor MTA1. HDAC1/HDAC2 subunits are histone deacetylase enzymes. Interacts directly or indirectly with methylated DNA.
ISWI family					
ISW1	ISW1	no	*S. cerevisiae*	4	Has nucleosome disruption and spacing activities.
ISW2	ISW2	no	*S. cerevisiae*	2	Has nucleosome spacing activity.
NURF	ISWI	?	*D. melanogaster*	4	Disrupts nucleosomes during transcriptional activation.
ACF	ISWI	?	*D. melanogaster*	2	Mediates chromatin assembly, spacing, and remodeling.
CHRAC	ISWI	?	*D. melanogaster*	5	Contains topoisomerase II. Has disruption and spacing activities.
RSF	hSNF2h	?	*H. sapiens*	2	Facilitates transcription from chromatin templates.

"Nucleosome disruption activity" refers to the ability of the factor to increase the accessibility of a nuclease to nucleosomal DNA. "Nucleosome spacing activity" refers to the ability of the factor to form a regularly spaced nucleosome array from randomly distributed nucleosomes. "Nucleosome remodeling activity" refers to the ability of the factor to alter the structure and/or position of a nucleosome.

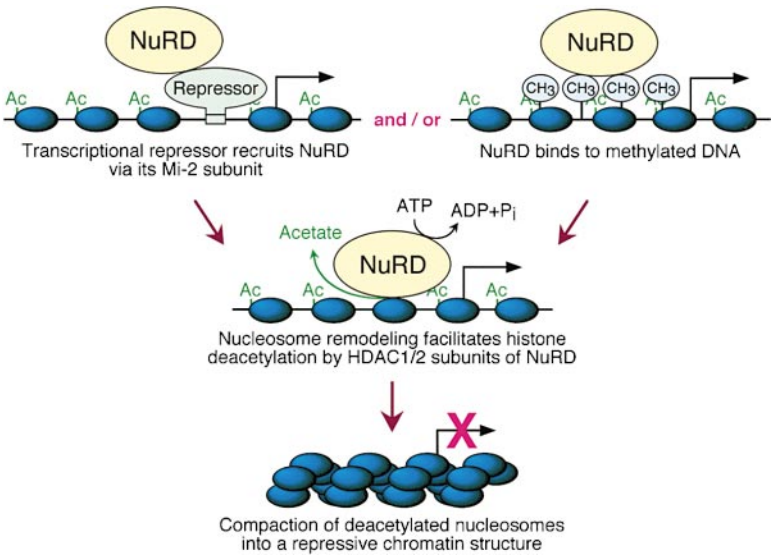

Figure 3. A Model for Transcriptional Repression by NuRD and Related Factors

NuRD (or NRD, NURD, or Mi-2 complex) is recruited to the chromatin template by its association with sequence-specific transcriptional repressors and/or methylated DNA. The nucleosome remodeling activity in NuRD facilitates histone deacetylation that may, in turn, promote the folding of chromatin into a repressed, higher-order structure.

in vitro and in vivo (Cosma et al., 1999; Di Croce et al., 1999).

Chromatin Remodeling Facilitates Transcriptional Repression

A DNA microarray analysis of global gene expression in yeast revealed that the SWI/SNF complex is important not only for transcriptional activation, but also for repression. Inactivation of the SWI/SNF remodeling complex altered the expression levels of 6% of all yeast genes, and surprisingly, most of the affected genes appeared to be negatively regulated by SWI/SNF (Holstege et al., 1998). Whether SWI/SNF influences directly or indirectly the expression of these genes is not known. Nevertheless, this genome-wide analysis suggests that SWI/SNF-catalyzed chromatin remodeling facilitates the function of transcriptional repressors as well as transcriptional activators (Figure 2).

Other recent findings support the hypothesis that the SWI/SNF complex and the related RSC complex participate in transcriptional repression. For instance, the RSC complex was found to be essential for repression of the yeast *CHA1* gene (Moreira and Holmberg, 1999). In addition, two human orthologs of SWI2/SNF2, BRG1 and hBRM, can bind to the Retinoblastoma (Rb) tumor suppressor gene product to inhibit the activity of the transcriptional activator E2F (Muchardt and Yaniv, 1999 and references therein). BRG1 also represses the endogenous human c-*fos* gene in concert with the Rb protein via a pathway that is independent of the E2F transactivator (Murphy et al., 1999).

NuRD/Mi-2 Complex, a Chromatin Remodeling Factor that May Repress Transcription by Histone Deacetylation

A direct and compelling link between transcriptional repression and chromatin remodeling has recently emerged in the discovery of the NuRD/Mi-2 complex (also known as NRD and NURD; Table 1; reviewed by Knoepfler and Eisenman, 1999 [this issue of *Cell*]). The NuRD/Mi-2 complex has both chromatin remodeling and histone deacetylation activities. The nucleosome remodeling activity of NuRD is required for NuRD-mediated deacetylation of histones in chromatin, which suggests that chromatin remodeling facilitates the access of the NuRD histone deacetylases to the histone tails (Figure 3). The transcriptional effects of NuRD-mediated histone deacetylation have not yet been tested, but histone deacetylation generally correlates with transcriptional repression. Inspection of the x-ray crystal structure of the nucleosome suggests that histone deacetylation might facilitate interactions between adjacent nucleosomes (Luger et al., 1997). Hence, in Figure 3, we have speculated that NuRD-mediated histone deacetylation promotes the formation of a higher-order, repressive chromatin structure.

The NuRD complex may be actively recruited to the genes that it represses (Figure 3). Interactions between the Mi-2 ATPase subunit of NuRD and sequence-specific transcriptional repressors have been observed (Kehle et al., 1998; Kim et al., 1999). In addition, NuRD appears to interact with CpG-methylated DNA and may thus participate in gene inactivation due to CpG methylation (see Bird and Wolffe, 1999 [this issue of *Cell*]).

Chromatin Assembly and Chromatin Remodeling Are Related Processes

Chromatin assembly and chromatin remodeling share some common features. Chromatin assembly involves the formation of nucleosomes from histones and DNA, whereas chromatin remodeling involves the disruption and re-formation of histone–DNA contacts. Thus, it was perhaps not surprising to find a factor, termed ACF, that mediates the ATP-dependent deposition of histones onto DNA (in conjunction with the NAP-1 histone chaperone protein) as well as the ATP-dependent mobilization of nucleosomes (in a process that does not require NAP-1) (Ito et al., 1997). This ability of ACF to catalyze both chromatin assembly and nucleosome remodeling may be a more general theme among chromatin remodeling complexes.

A connection between chromatin assembly and gene expression has been observed in studies of CAF-1 (chromatin assembly factor-1; reviewed in Adams and Kamakaka, 1999) and RCAF (replication-coupling assembly

factor; Tyler et al., 1999) in *S. cerevisiae*. Both CAF-1 and RCAF are non-ATP-utilizing chromatin assembly factors that bind to histones H3 and H4. Loss of CAF-1 (by disruption of the *CAC1* gene encoding the largest subunit of CAF-1) results in the partial derepression of transcriptionally silenced genes at telomeres or at the silent mating type loci, whereas loss of RCAF (by disruption of the *ASF1* gene encoding the largest subunit of RCAF) had little or no effect upon transcriptional silencing. The simultaneous loss of CAF-1 and RCAF, however, causes complete derepression of genes in silenced chromatin. Thus, the chromatin assembly factors CAF-1 and RCAF appear to participate in the assembly of transcriptionally repressive chromatin in yeast. It will be interesting to investigate the functional interplay among CAF-1, RCAF, and ATP-utilizing chromatin remodeling complexes during chromatin assembly and transcriptional repression.

Conclusions and Prospects

In summary, chromatin remodeling complexes facilitate nucleosome assembly and mobilization by their ability to break and to reestablish histone–DNA contacts. In the future, it will be particularly interesting to elucidate the specific functions of each of these remodeling factors, which will participate in nucleosome assembly and/or mobilization during transcriptional activation or repression, DNA repair, DNA replication, recombination, or any other nuclear event that occurs in the context of nucleosomes. Even the dark side of chromatin remodeling appears to have a bright future.

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