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Minireview

Transcription factor-mediated chromatin remodelling: mechanisms and models

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Abstract The association of DNA with nucleosomes in chromatin severely restricts the access of the regulatory factors that bring about transcription. In vivo active promoters are characterised by altered, almost transparent chromatin structures that allow the interaction of the transcriptional machinery. Recently, enzymatic activities have been discovered that facilitate the binding of transcription factors to chromatin by modifying nucleosomal structures in a process that requires energy. The mechanisms by which chromatin is remodelled may involve nucleosome movements, their transient unfolding, their partial or even complete disassembly. The dynamic properties of chromatin that underlie these structural changes are fundamental to the process of regulated gene expression.

Key words: Chromatin; Transcription; SWI/SNF complex; Nucleosome; Regulation

1. Nucleosomes repress transcription by limiting the access of transcription factors

A large body of evidence has been accumulated both from in vivo and in vitro experiments over recent years that the organisation of DNA in chromatin establishes a *de fault* repressed state for transcription ([1,2] and references therein). The wrapping of the DNA around nucleosomes restricts the access of DNA binding proteins such as transcription factors to their target sequences (reviewed in [3]). In nuclei active promoters are usually marked by discontinuities in the ordered array of nucleosomes. Increased access at those sites correlates with the binding of transcription factors [4,5] but the causalities are still not resolved: do specialised transcription factors themselves open up chromatin or do dedicated mechanisms exist that alter nucleosome structures such that transcription factors can bind?

The best illustration of the repressive character of chromatin and the reorganisation of nucleosome arrays upon interaction of transcription factors has been obtained in yeast. Yeast strains have been constructed in which transcription of histone genes can be conditionally inhibited such that histones become limiting in the cell. The depletion of nucleosomes resulted in the uncontrolled activation of a selected number of previously repressed, but inducible genes [6]. The conclusions from these experiment were, that nucleosomes contribute to the repression of these genes and that part of the activation mechanism may involve nucleosomal rearrangements. A paradigm for such a situation is the regulation of the *PHO5* gene by phosphate starvation. Induction of *PHO5* is accompanied by the loss or drastic modification of four positioned nucleosomes over the promoter, an example of chromatin remodelling that requires neither replication nor transcription of the gene (reviewed in [7]). Chromatin remodelling critically depends on the induced binding of the transcription factor PHO4 to a low affinity binding site between the target nucleosomes. Nucleosome destabilisation is thus initiated from within a linker sequence in a reaction that requires the transactivation domain of PHO4 [8,9]. The precise mechanisms by which PHO4 and other transcription factors known to mediate chromatin rearrangements in vivo, such as GAL4 in yeast and the glucocorticoid receptor in mammalian cells, open up promoters are still unknown (reviewed in [5]).

DNA replication perturbs the chromatin structure and may provide a window of opportunity for transcription factors to compete with nucleosomes for binding sites. However, transcription factor-associated chromatin rearrangements frequently do not require replication [10–12]. A recent study in yeast [13] demonstrated that for ribosomal RNA genes the chromatin configuration of the actively transcribed genes cannot be directly inherited after replication. Instead the newly synthesised strands are first packaged into *regular* arrays of nucleosomes. The regeneration of the active chromatin structure, at least in this case, is a post-replicative event that presumably involves disruption of pre-formed nucleosomes.

2. SWI/SNF complexes: enzymatic activities that open chromatin

Genetic analyses in yeast have identified the SWI/SNF complex as a candidate activity that helps transcriptional activators like GAL4 to overcome chromatin-mediated repression. This complex is composed of at least 10 subunits, some of which have been molecularly identified [14]. The SWI-SNF complex mediates transcriptional activation in vivo of a range of inducible genes and mutations in SWI/SNF genes show pleiotropic phenotypes (reviewed in [15]). The observation that mutations in histone H3 or the deletion of one of the two H2A/H2B gene clusters in yeast suppress mutations in SWI/SNF genes revealed the role of the SWI-SNF complex in chromatin remodelling [14,16]. Genes that are homologous to SWI/SNF components have been identified in yeast, *Drosophila*, cattle and man (reviewed in [17]). The recent identification of proteins with struc-

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tural or functional similarities to SWI/SNF factors suggests the existence of more than one complex involved in global activation of transcription in chromatin [18,19].

3. The biochemistry of SWI/SNF function

Analysis of SWI2, an integral component of the SWI/SNF complex, has revealed a hint about its mode of action: SWI2, in isolation or as part of the entire complex has a DNA-dependent ATPase activity as predicted from sequence similarities to other ATPases [20,21]. Using a model system, Workman, Peterson and coworkers demonstrated that ATP hydrolysis was required for the surprising property of the purified complex to stimulate the binding of the yeast transcriptional activator GAL4 to nucleosomal DNA [22]. In these experiments the SWI/SNF complex contacted the nucleosome directly and altered the positioning of the nucleosomes with respect to the underlying DNA sequence in a way that could indicate either nucleosome movements or massive rearrangements of nucleosome structure. Interestingly, nucleoplasmin, a histone chaperone and nucleosome assembly factor, had a synergistic effect with SWI/SNF in facilitating the binding of GAL4 to nucleosomal DNA. It has been shown earlier that nucleoplasmin can stimulate the binding of transcription factors to nucleosomes by specifically removing histones H2A and H2B from the core particle [23]. The observed synergism suggests that SWI/SNF also acts via partial disassembly of the nucleosomal core.

Partially purified human SWI/SNF complex also mediates ATP-dependent nucleosome reorganisation, which enables GAL4 derivatives and the TATA-binding protein (TBP) to interact with nucleosomal DNA [24,25]. A difference between the experiments with yeast or human SWI/SNF complex is that in the latter case the ability of GAL4 to associate with nucleosomal DNA was positively influenced by the presence and strength of the acidic activation domain (which does not influence GAL4 binding to naked DNA or nucleosomal templates in the absence of SWI/SNF) whereas in the experiments by Coté et al. no effect of the transactivation domain was noted. Gel electrophoresis of protein-DNA complexes did not reveal a massive nucleosome disruption [25]. The fact that the facilitated interaction of TBP with nucleosomal DNA depended on the specific surface orientation of the TATA box also suggests that some kind of nucleosomal structure persists in the presence of SWI/SNF and ATP. SWI/SNF action on circular plasmid chromatin resulted in an altered linking number which may result from an unwinding of DNA from the nucleosome surface or a change of the helical twist of the DNA, as might be brought about by histone acetylations (reviewed in [26]).

These in vitro studies suggest that the SWI/SNF complex

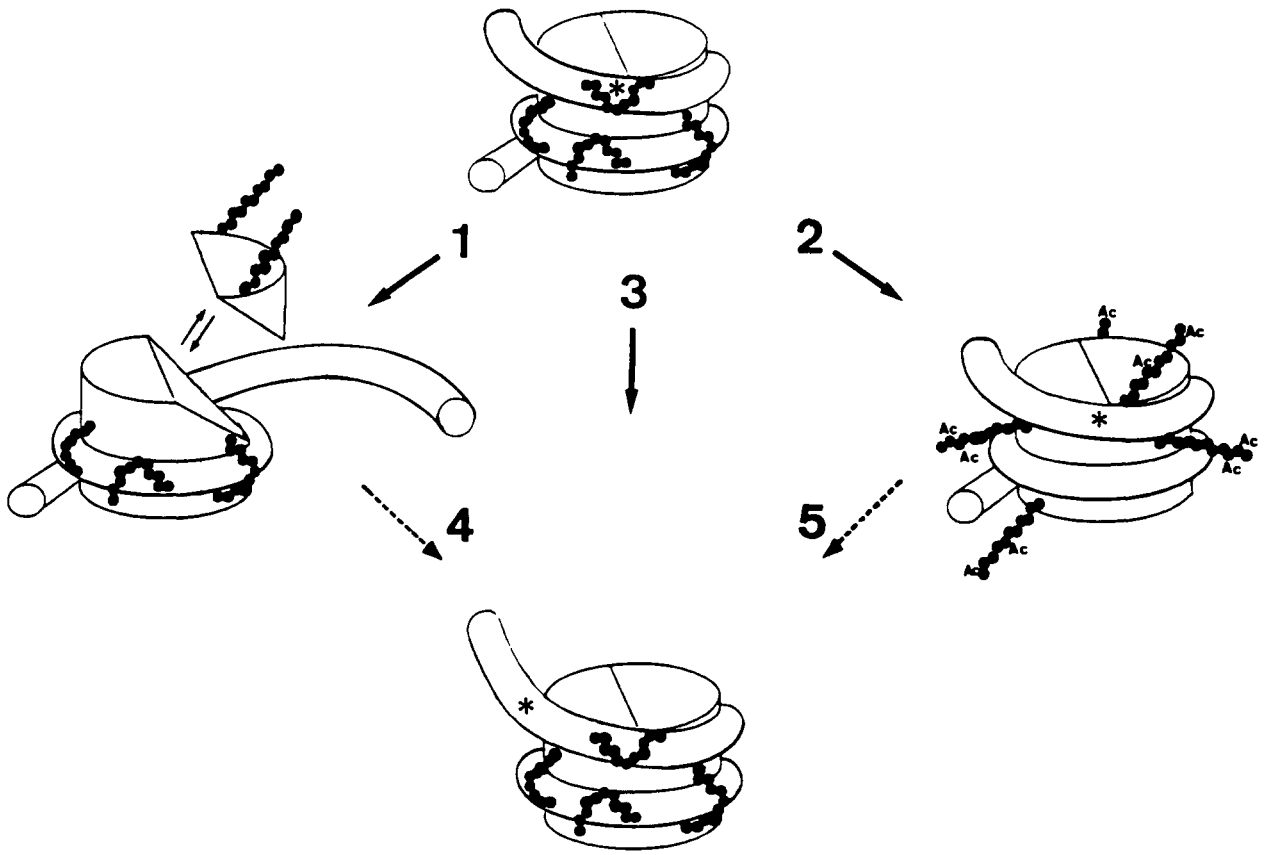

Fig. 1. Schematic representation of the different modes of generating access to a nucleosomal target sequence. A particular sequence on the nucleosomal surface (asterisk) can be rendered accessible by a variety of mechanisms: (1) The removal of one H2A/H2B dimer from the nucleosome core will free a certain stretch of DNA. (2) The acetylation (Ac) of lysine residues in the histone N-termini (black coils) will weaken the 'histone tail'-DNA association. (3) Nucleosome sliding renders the target sequence accessible in the nucleosomal linker. (4 and 5) The weakening of histone/DNA contacts is likely to promote nucleosome mobility. Therefore sliding of the nucleosome may be increased by either tail acetylation or transient removal of H2A/H2B.

specifically affects nucleosomal DNA. However, SWI/SNF may have additional activities, since antibodies against SWI3 have been shown to affect transcription in a cell-free system that lacked nucleosomal templates [27]. It would not be surprising if it turned out that this huge 2 MDa complex contained more than just one activity [14].

4. Creating access by nucleosome unfolding or disassembly

How could the nucleosome structure be altered to facilitate the interaction of transcription factors? The histone octamer is a tripartite protein assembly composed of a centrally located and more strongly bound $(H3\text{-}H4)_2$ tetramer flanked by two H2A-H2B dimers [28]. This modular nature, allows for a stepwise assembly and disassembly of the nucleosome core. Evidence for the existence of 'unfolded' nucleosomes or subnucleosomal particles under special circumstances has been accumulated over the years. Nucleosomes in transcriptionally active genes are characterised by an enhanced accessibility of sulfhydryl groups on H3 [29,30] and near the dyad axis [31]. Nucleosomes from actively transcribed genes that can be trapped in association with RNA polymerase II are deficient in one H2A-H2B dimer [32]. These and other observations led Van Holde et al. to suggest that actively transcribed genes may contain nucleosomes which are (perhaps transiently) devoid of one H2A-H2B dimer [33] (see Fig. 1). H2A-H2B dimers are more easily displaced from the histone core than H3 and H4 [34] and extensive exchange of these dimers occurs in vivo [35]. Studies with the intercalator ethidium bromide demonstrated that a change in DNA topology close to the nucleosome results in a specific loss of H2A-H2B. The unwinding of DNA upon intercalation of the dye resulted in a slow and reversible dissociation of histones, initiated by the leave of one H2A-H2B [36,37]. The depletion of H2A-H2B from the nucleosome has profound implications on the association of transcription factors, such as TFIIIA, with nucleosomal DNA [38].

5. Creating access by histone modifications

Flexible, highly positively charged N-terminal 'tails' of all four core histones and the C-terminal tails of H2A protrude from the compact core and display sites that are modified by acetylation, phosphorylation and ubiquitination depending on the functional status of chromatin (reviewed in [39]). Due to their interaction with DNA on the nucleosome surface as well as in the linker DNA [40,41] these tails may restrict the access of transcription factors to nucleosomal DNA [42,43]. The repressive effects of the N-termini can be overcome by at least two possible mechanisms: (i) Their acetylation weakens the interaction with nucleosomal DNA leading to increased access [42] (see Fig. 1). (ii) The interaction of factors with DNA at the nucleosome edge appears less restricted by the N-termini than the interaction with DNA at the nucleosome dyad. Starting with binding to peripheral sites, disparate transcriptional activators can co-operate to 'invade' a nucleosome such that eventually internal site are occupied in the presence of the tails [44].

6. Creating access by increasing the mobility of nucleosomes

Studies in a crude chromatin assembly extract derived from *Drosophila* embryos have pointed to an additional mechanism by which the interaction of transcription factors with chromatin could be facilitated: nucleosome movements [45]. A number of studies have documented that a variety of transcription factors, such as GAGA factor, Heat Shock Factor and GAL4-VP16 can rearrange nucleosomes on promoters reconstituted in *Drosophila* embryo extracts [46–48]. Interestingly, these nucleosome rearrangements require an extract activity that hydrolyses ATP. While this fact is reminiscent of the ATP-dependent action of the SWI/SNF complex, presently the identity of this activity is not known. Studies in our lab suggested that nucleosome movements may be involved in chromatin rearrangements: not only do nucleosome movements occur in chromatin reconstituted in the *Drosophila* system, they are also facilitated by ATP hydrolysis [45]. Under those conditions chromatin is maintained in a state of generally increased access that requires continuous energy utilisation. Taking nucleosome mobility into account, chromatin rearrangements by transcription factors can be explained by the nucleosome sliding off a particular DNA target and must not necessarily involve their disruption [45,48]. Nucleosome mobility is an intrinsic property of nucleosomes and can be understood as Brownian motion of the DNA superhelix around the histone core [49,50].

Fig. 1 summarises current ideas on how access of transcription factors to nucleosomal DNA may be increased. This may be achieved by acetylations of the histone tails that influence the tightness of their DNA interactions. The removal of one H2A/2B dimer from the nucleosome core may either suffice to allow the interaction of transcription factors, or be only a first step in a more extensive disassembly reaction. Little is known how nucleosomes are rendered mobile, but clearly, any modification that decreases histone/DNA contacts, such as histone tail acetylation and the transient removal of an H2A/2B dimer, is expected to facilitate nucleosome movements. The two apparently distinct principles may therefore both be mechanistically connected in the series of events that lead to the reorganisation of nucleosomal DNA by transcription factors.

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