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Mechanism of nucleosome disruption and octamer transfer by the chicken SWI/SNF-like complex

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Abstract

We had recently characterized SLC, a SWI/SNF-like chromatin remodelling activity, from chicken liver. The SLC efficiently disrupts nucleosomes, transfers histone octamers from nucleosomal substrates onto acceptor DNA, and slides histone octamers along DNA. Here, we present evidence that SLC is indeed a SWI/SNF homologue, and it disrupts nucleosomes by inducing extensive dynamic helical distortions in the nucleosomal DNA. Both the nucleosome disruption and octamer transfer functions are indifferent to nucleosomal histone tails. We further show that the nucleosome disruption precedes the octamer transfer and that the latter requires continuous presence of ATP. Based on these observations, we propose that a disrupted nucleosome is not a spontaneous substrate for octamer transfer; rather the nucleosome disruption and the octamer transfer are two temporally successive, ATP-dependent events during nucleosome remodelling by SLC in vitro.

Keywords: Chromatin remodelling; Nucleosome disruption; Octamer transfer; SWI/SNF-like complex

The chromatin organization offers the platform for controlled folding/unfolding of the genome, which in turn ensures precise regulation of gene expression [1,2]. Such reconfiguration of the chromatin domains is mediated largely by two disparate functions attributable to distinct multicomponent enzymes that are evolutionarily conserved [3–5]. On one hand, covalent modifications of the chromatin constituents mark distinct chromatin domains for structural and functional distinctiveness [6,7]; many of these modifications, if not all, are understood to be reversible. On the other hand, ATP-dependent restructuring of chromatin domains makes the DNA more accessible to regulatory proteins [8,9]. Though the past couple of years has seen tremendous unravelling of information regarding the modes and mechanisms of chromatin reconfiguration, the precise mechanism of action of each of the ATP-dependent chromatin remodellers awaits elucidation [9].

Each of the ATP-dependent chromatin remodellers contains a central ATPase component belonging to the SNF2 family of ATPases [10]. These ATPase components alone can carry out subsets of remodelling functions that are characteristics of the respective remodelling factors [11–14]. Depending upon the assay system used, subsets of these remodellers and their ATPases render nucleosomes hypersensitive to nucleases, facilitate transcription factor binding to nucleosomes, stimulate transcription in vitro and in vivo, mobilize nucleosomes along DNA, induce negative superhelical change in circular polynucleosomes, transfer histone octamers onto extraneous DNA, and translocate DNA [9,14–16].

While all these seemingly disparate functions are not exhibited in vitro by all the remodelling factors known till date, a few of the remodelling factors have been tested in parallel in different assay systems. Remodelling factors belonging to SWI/SNF and Mi-2 subfamilies make nucleosomes hypersensitive to DNase

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I, an activity not exhibited by the ISWI-containing complexes. Though there is no direct explanation for the nuclease hypersensitivity as yet, it is understood that a propagative change in the DNA helicity, with or without an associated change in writhe, or a consequent change in translational positioning, can expose regions of nucleosomal DNA that are otherwise inaccessible to the nuclease [9,17]. Recent observations suggest that the human SWI/SNF induces transient but global disruption of histone–DNA contacts [18]. Another remarkable function of the SWI/SNF-group of remodellers is transfer of histone octamers from nucleosomal substrates to extraneous DNA, an activity so far reported only for yeast RSC and human SWI/SNF [19–21]. We have recently observed a similar octamer transfer activity in a SWI/SNF-like nucleosome remodelling complex SLC from chicken liver [22]. Here, we present some analyses of nucleosome disruption (DNase I hypersensitivity) and octamer transfer functions of SLC. Using uniformly labelled nucleosomes, we demonstrate that SLC induces extensive, rapid, and dynamic alteration in the helical periodicity of the nucleosomal DNA. Detectable nucleosome disruption is accomplished in a minute, whereas detectable octamer transfer requires at least 10 min of reaction. We further show evidence that the nucleosome disruption and the octamer transfer are two temporally successive, ATP-dependent events during nucleosome remodelling by SLC in vitro. Additionally, the nucleosome disruption and the octamer transfer functions are indifferent to nucleosomal histone tails.

Materials and methods

Nucleosome reconstitution and purification. Fragments containing TG motif [23] were used for nucleosome reconstitution. A 151 bp fragment (TG-151) was generated by *Eco*RI–*Hin*dIII double digestion of pTG, labelled at both ends with [α-^{32}P]dATP, reconstituted into nucleosomes (Nu151), and was used for octamer transfer reactions. A 209 bp fragment was generated by PCR using SP6 and T7 promoter primers in the presence of [α-^{32}P]dATP. This uniformly labelled fragment (F209) was reconstituted into nucleosomes (Nu209) and was used for nucleosome sliding reactions. F209 was further double-digested with *Eco*RI and *Hin*dIII to obtain a uniformly labelled 151 bp fragment, which was reconstituted into nucleosomes for nucleosome disruption reactions. Preparation of H1-depleted soluble chromatin, nucleosome reconstitution, and purification were performed as described [22]. Tailless nucleosomes (Nuc^{tr}) were reconstituted with trypsinized donor chromatin. Soluble chromatin from mouse liver was trypsinized and purified as described [24].

Partial purification of SLC. Partial purification of SLC was as described [22]. Briefly, purified nuclei from chicken liver were extracted with SSB-0.5 (15 mM Tris–HCl, pH 7.5, 10% glycerol, 0.1 mM EDTA, and 0.1% Tween 20 with 0.5 M KCl). The extracts were applied onto cellulose phosphate column. The 0.5 M eluate was applied onto DEAE–Sephacel and eluted with 0.3 M KCl. This eluate was concentrated and fractionated on Sepharose CL-6B. Elution of SLC was monitored by Western blotting using antibodies against human SWI/SNF components BRG1, BAF170, BAF155, and BAF57. SLC (fractions 9–12) was aliquoted and stored frozen at −70 °C.

Nucleosome disruption. Disruption assay was performed as described [22]. Purified positioned nucleosomes (Nu151, uniformly labelled; 20,000 cpm; 0.5–1.0 ng DNA) were incubated with 5 μl SLC in a final buffer composition of 15 mM Tris–HCl (pH 7.5), 45–60 mM KCl, 3–5 mM $MgCl_2$, 1–3 mM Mg^{2+}–ATP, 5–7.5% glycerol, 0.05 mM EDTA, 100 μg/ml BSA, and 0.05% NP-40 at 30 °C for different time points. Thereafter, nucleosomes were digested with 0.1 U (or more, see figure legend) DNase I at 30 °C for 1 min. The digests were deproteinized with proteinase K, ethanol-precipitated, denatured, resolved on an 8% polyacrylamide–7 M urea denaturing gel, and autoradiographed. For naked DNA controls, the probes were digested with 2.5 mU of DNase I in the presence of 50 ng soluble chromatin in 20 μl in the same buffer composition as for the nucleosomes.

Nucleosome sliding. Nucleosomes reconstituted on uniformly labelled 209 bp TG fragment (Nu209, 5000 cpm, ~2 ng) were treated with 5 μl SLC, in identical buffer condition as for disruption reactions, for 45 min at 30 °C. SLC was titrated with excess soluble chromatin before electrophoresis of samples at room temperature in a 5% native PAGE in 10 mM Tris–HCl–1 mM EDTA (pH 8.0) with constant buffer recirculation.

Octamer transfer. Purified Nu151 (labelled at both ends, 5000 cpm, ~0.2 ng) were incubated with 5 μl SLC in the presence of 10 ng oligonucleosomal DNA in a buffer composition identical to the reaction condition used for nucleosome disruption (see above). Conversely, TG-151 (labelled at both ends; 5000 cpm, ~0.2 ng) were incubated with 5 μl SLC as above in the presence of 10 ng soluble chromatin. The reaction was carried out at 30 °C for different time points as indicated. Also, 0.5 U apyrase was added to the reaction at different time points as indicated in the figure legend to deplete ATP. The reaction was stopped with addition of soluble chromatin in excess. The products were resolved on 5% native PAGE in 0.5× TBE buffer.

Results and discussion

Octamer transfer function is attributable to the SWI/SNF-like complex

We have recently characterized a ~2 MDa chromatin remodelling activity (viz., nucleosome disruption, octamer transfer in *trans*, and nucleosome sliding) from chicken liver [22]. This activity co-elutes with immunoreactivity to antibodies against human SWI/SNF components and hence was named SLC (for SWI/SNF-like complex) [22]. Since SLC was not affinity-purified, its preparation may contain remodelling factors other than those belonging to the SWI/SNF group. However, it logically excludes the smaller ISWI-group remodellers as the final step of enrichment was a gel-filtration chromatography. Further, SLC can remodel tailless nucleosomes unlike the ISWI-group remodellers (see below). Therefore, to narrow down the identity of SLC, we have incubated SLC with anti-BRG1 antibodies prior to octamer transfer and nucleosome sliding reactions. Both the octamer transfer and the nucleosome sliding functions are abolished if the SLC preparation is preincubated with antibodies against hSWI/SNF component BRG1 (Fig. 1). Similar inhibition was observed with antibodies against other hSWI/SNF components BAF170, BAF155, and BAF57, but not against the anti-ISWI antibodies (data not shown), suggesting that both

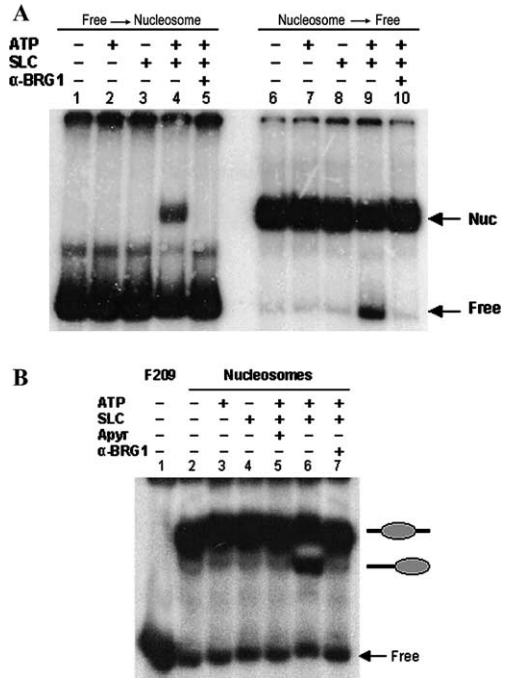

Fig. 1. Specific inhibition of octamer transfer by anti-hBRG1 antibodies. (A) Anti-hBRG1 antibodies inhibit octamer transfer. Octamer transfer reactions from cold donor chromatin (20 ng in lanes 1–5 each) onto labelled TG-151 fragments (Free) and from labelled nucleosomes onto cold acceptor DNA (20 ng in lanes 6–10 each) were carried out. SLC transfers octamer onto free DNA (lane 4) and from labelled nucleosomes (lane 9) in the presence of ATP. Octamer transfer is inhibited when the reaction mixture is incubated with 1 μl of anti-hBRG1 J1 antibody for 30 min at 30 °C prior to addition of ATP (compare lane 4 to 5 and lane 9 to 10). (B) Centrally positioned nucleosomes reconstituted on 209 bp TG fragments were subjected to nucleosome sliding reaction by SLC. Nucleosomes slid to DNA termini (lane 6) migrate faster than the centrally positioned ones. This reaction is also inhibited by incubating the reaction mixture with 1 μl of anti-hBRG1 J1 antibody for 30 min at 30 °C prior to addition of ATP (compare lane 7 to 6). Illustration on right indicates position of the nucleosomes.

these functions are indeed attributable to the chicken counterparts of SWI/SNF.

SLC inflicts dynamic alteration in nucleosomal DNA topology

A subset of all the groups of chromatin remodelling factors render asymmetrically end-labelled nucleosomes hypersensitive to DNase I, an activity referred to as 'nucleosome disruption.' Such nuclease-hypersensitivity is believed to be the consequence of alteration in the helical path of DNA around the histone octamer. This view is supported by evidences that certain remodellers induce negative superhelical torsion in chromatin and change the nucleosomal DNA topology [25,26]. Though these nucleosomes on disruption appear to display hypersensitivity to DNase I throughout their length, it is difficult to conceptualize such global helical alteration in a single nucleosome. This pattern, therefore, most likely represents a population of nucleosomes that have acquired localized distortions (local change in rotational phasing or dissociation of DNA from octamer surface) at different regions along the DNA in different nucleosomes. To test this hypothesis, we have subjected uniformly labelled nucleosomes to disruption by SLC.

Because of uniform labelling throughout, fragments generated from any two intranucleosomal cuts will also be visible. If there will be any distortion at a precise location along the nucleosomal DNA in a synchronous population, this assay would still generate predominant 10 nt-periodicity, albeit with a small amount of smear. Second, if the nucleosomal DNA has undergone non-uniform helical distortion throughout the superhelix in an asynchronous population, that is, extensive localized helical distortion (involving non-integral helical rotation) all over the nucleosomal length in different nucleosomes, the 10 nt periodicity will be lost. Third, however, if the helical rotation is non-integral, but is so synchronous that all the bases or regions along the nucleosomal DNA would rotate simultaneously to similar extent, this periodicity will remain unaltered. Such a possibility is infeasible, since the superhelical twist (and associated writhe) will not allow all the regions along the DNA to rotate synchronously and simultaneously. Moreover, this would require all nucleosomal histone–DNA interactions to disrupt simultaneously and then reinstate; a feat mechanically infeasible.

Fig. 2A depicts that the 10 nt-periodicity of DNase I cleavage of uniformly labelled nucleosomes is lost when the nucleosomes are treated with SLC and ATP. As discussed above, this observation suggests that SLC generates localized helical distortions along the nucleosomal DNA. Now, if the distortion originates at one location and propagates in any direction, the progressive wave of distortion can be trapped by a DNase I cleavage, generating fragments of all possible length. In other words, such helical dynamism will either shorten or lengthen the distance between two adjacent cuts depending on (i) direction of propagation of the distortion and (ii) position of the second cut in consideration. Then, controlled increase in the temporal and spatial frequency of DNase I-induced cuts will restore the 10 nt-periodicity; because the fragment length-heterogeneity will be diminished by higher frequency of DNase I cuts. Indeed, increasing the DNase I amount for digestion of SLC-remodelled uniformly labelled nucleosomes reinstates the characteristic 10 nt-periodicity (Fig. 2B, compare lane 1 to lane 10, and lane 10 to lanes 11–13). This explains why in an earlier attempt no SWI/SNF-disruptibility was evident on uniformly labelled nucleosomes [27]. These observations suggest that SLC dynamically alters the topology of nucleosomal DNA. Here, different remodelled nucleosomes in a population will have different regions of their DNA distorted to varying extent. These alterations may very well involve

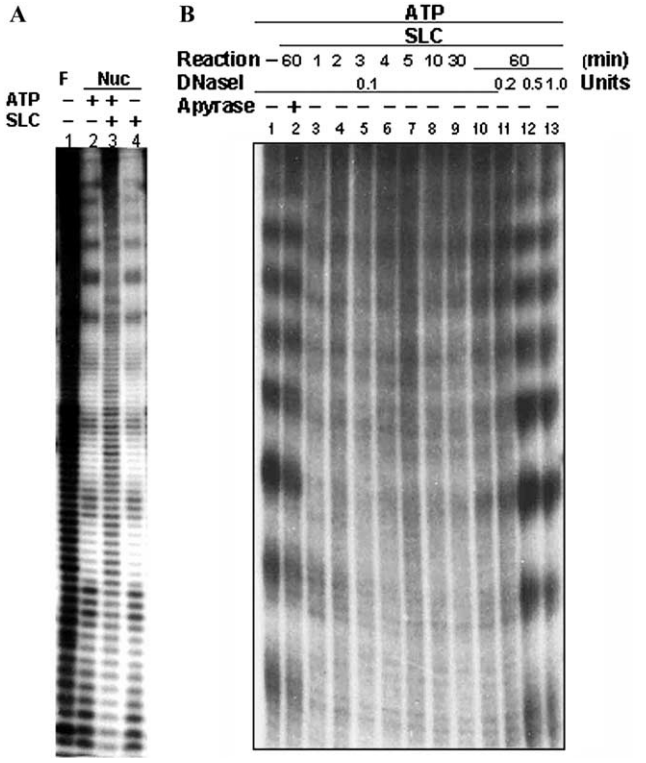

Fig. 2. Disruption of uniformly labelled nucleosomes by SLC. (A) Uniformly labelled nucleosomes (151 bp) treated with ATP and SLC as indicated, digested with 0.1 U DNase I for 1 min at 30 °C, deproteinized, and resolved on a 7 M urea–8% denaturing PAGE. (B) Time kinetics and DNase I-dose kinetics of nucleosome disruption by SLC. Nucleosomes were digested with 0.1 U DNase I after treatment with SLC for 1–60 min (lanes 10). Nucleosomes subjected to SLC remodelling for 60 min were digested with 0.1–1.0 U of DNase I (lanes 10–13). Increased DNase I-digestion of remodelled nucleosomes reinstates the 10 nt-periodicity.

formation and propagation of a loop or a bulge as suggested (see [9] for a discussion) and translocation of nucleosomal DNA as well [14]. This observation is consistent with a recent report revealing generation and interconversion of multiple nucleosomal states during remodelling ([28]; see [41] for a discussion).

Nucleosome disruption and octamer transfer are two temporally successive, active events

The nature of the remodelled nucleosome has remained elusive. It is argued that the remodelled nucleosome is an activated and unstable state, which collapses into a number of possibilities including (i) a non-covalent dimer [29,30], (ii) a nucleosome relocated translationally (see [16] for a review), or (iii) formation of a hybrid nucleosome wherein the octamer has been transferred to an extraneous piece of DNA [19–22]. It was proposed that the remodellers could slide nucleosomes along DNA, or unwrap the nucleosomes at the DNA termini [20,31,32]. Two such remodelled nucleosomes that have a portion of their octamer devoid of DNA-contact (see state 2 in Fig. 3) may interact to form a stable non-covalent dimer (state 3 in Fig. 3). Whether this reaction is spontaneous or is accomplished actively by the remodeller is not clear, though reversibility of the reaction argues for active generation of the dimer by the remodeller [30]. However, formation of hybrid nucleosomes (see state 4 in Fig. 3) by transfer of histone octamers onto extraneous DNA is believed to be an extreme consequence of the mechanism that generates non-covalent dinucleosomes (see [9] for a discussion). Since the remodelled nucleosomes (with altered DNA topology, altered octamer–DNA interactions, and unwrapping of DNA from the octamer surface) are considered unstable, an excess of extraneous DNA may compete with the existing nucleosomal DNA and eventually titrate it out (see Scheme B in Fig. 3). We have addressed this possibility here and present evidence that the octamer transfer is instead an active process rather than spontaneity.

It is known that the remodelled state of a nucleosome persists for several hours even after depletion of ATP or detachment of the remodeller from the nucleosome [27,33,34]. Therefore, stopping the remodelling reaction at different time points and supplementing the reaction with excess of competitor DNA should lead to the formation of hybrid nucleosomes. To test this hypothesis, we first sought to know the time kinetics of remodelling

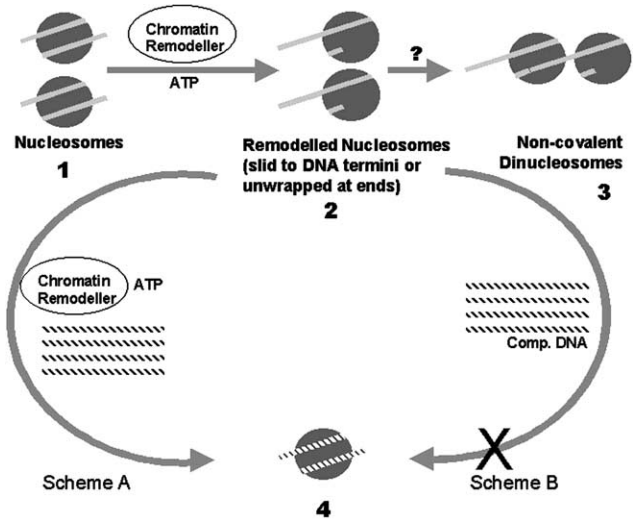

Fig. 3. An illustration of nucleosome remodelling depicting formation of a non-covalent nucleosome-dimer, or a hybrid nucleosome by means of octamer transfer. Nucleosomes (state 1) can be remodelled to a state wherein they are slid to DNA termini, are topologically distorted, and have portion of octamer surface devoid of DNA-contact (state 2), likely represented by the nuclease-hypersensitive nucleosome. Such remodelled nucleosomes can interact to form non-covalent dimers (state 3), or the octamers thereof can be transferred onto extraneous competitor DNA (Comp. DNA) either spontaneously (Scheme B) or actively by a chromatin remodeller (Scheme A) leading to formation of hybrid nucleosomes (state 4). We propose that the octamer transfer is instead an active process (see text).

(based on disruption of 10 nt-periodicity of uniformly labelled nucleosomes) and octamer transfer. Fig. 2B (compare lane 1 to lanes 3–10) shows that loss of 10 nt-periodicity is detectable even after a minute of remodelling reaction. The experimental strategy for the kinetics of octamer transfer employed both the free probe → nucleosome (Fig. 4, lanes 1–10) and nucleosome → free (Fig. 4, lanes 11–20) conversion reactions. As opposed to the nucleosome disruption reaction, the octamer transfer is not detectable until 10 min of reaction (data not shown; see Fig. 4, lanes 4 and 14 as compared to lanes 1 and 11, respectively), suggesting that nucleosome disruption precedes octamer transfer in a remodelling reaction in vitro. The extent of octamer transfer increased up to 30 min of reaction and no further transfer was noticed thereafter up to 60 min (Fig. 4, lanes 4–6 and 14–16). However, in a course of 60 min of reaction, addition of apyrase at 0 and 5 min inhibited octamer transfer (lanes 7, 8 and 17, 18). Instead, when apyrase was added to the reaction after 10 and 30 min, the extent of octamer transfer was detectably comparable to similar conditions wherein there was no apyrase (compare lanes 9, 10 and 19, 20 to lanes 4, 5 and 14, 15, respectively). These observations clearly suggest an active pathway for octamer transfer in vitro in the presence of the remodeller, ATP and competitor DNA (Scheme A in Fig. 3) rather than spontaneity (Scheme B therein), which succeeds nucleosome disruption. This observation is consistent with predicted involvement of hSWI/SNF in octamer transfer [21].

It can be argued that transferring an octamer in *trans* would be an extreme feat requiring considerable input of energy. Therefore, the first step during remodelling would be to reconfigure the nucleosome so as to destabilize it, lowering the energy barrier eventually required for octamer transfer. It is possible that octamer transfer hereafter might not be such a time consuming reaction as evident in this report, but the sensitivity of the assay systems used for both these steps differ. Note that such a possibility does not argue against the disruption and the octamer transfer being temporally successive. However, further quantitative analysis of the reaction mechanism was hindered as the SLC was not affinity purified and the nucleosome preparations contained considerable labelled free DNA and donor chromatin as well. Dose kinetic analyses of the substrate and the enzyme were also not feasible because of the same reasons.

Remodelling by SLC is indifferent to histone tails

The N-terminal tails of histones play crucial roles in establishment and maintenance of definitive structural and functional chromatin domains [7,35,36]. Lysine-methylation of histone H3 at position 4 disrupts interaction of the chromatin remodeller NuRD with nucleosomes [37]. Though the SWI/SNF-group remodellers [24,38] and the *Drosophila* Mi-2 complex [39] can remodel tailless nucleosomes, the ISWI-group remodellers require at least the histone H4 N-terminus intact [40]. Therefore, we sought to see if SLC could remodel nucleosomes that lack their N-terminal tails (tailless nucleosomes). To reconstitute tailless nucleosomes, donor chromatin was trypsinized and purified as described [24]. Along with the normal nucleosomes, the tailless nucleosomes (Nuc^{tr}) were subjected to disruption (Fig. 5A) and octamer transfer (Fig. 5B) reactions. The tailless nucleosomes revealed no differences from normal nucleosomes in terms of disruptibility and octamer transfer by SLC, indicating that SLC function is indifferent to the nucleosomal histone tails. This observation further argues against involvement of any ISWI-group remodeller in the SLC preparation.

The work presented here is informative regarding two aspects of chromatin remodelling. It suggests that the 'nucleosome disruption' is indeed indicative of collective randomization of DNA topology in a nucleosome population. Arguably, such randomization of DNA topology can only be localized in small stretches, rather than total collapse of DNA topology throughout a single nucleosome. Therefore, at any given time point during remodelling, different regions of nucleosomal DNA will assume different helical geometry on different

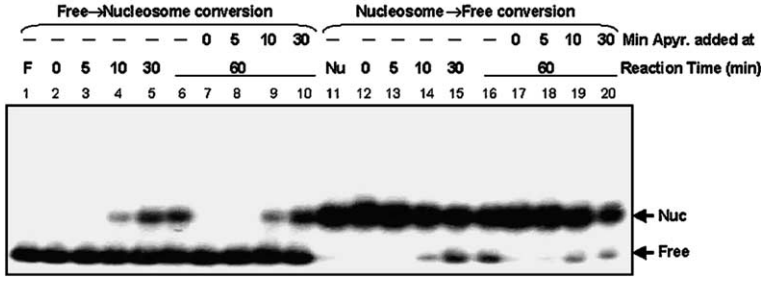

Fig. 4. Kinetics of octamer transfer. Labelled TG-151 fragments (Free) were incubated with donor chromatin, SLC, and ATP for 0, 5, 10, 30, and 60 min (lanes 2–10). Conversely, labelled Nu151 nucleosomes (Nuc) were incubated with acceptor DNA, SLC, and ATP for 0, 5, 10, 30, and 60 min (lanes 12–20). Apyrase (0.5 U) was added to scavenge ATP at 0 (lanes 7, 17), 5 (lanes 8, 18), 10 (lanes 9, 19), and 30 (lanes 10, 20) min of the reaction. The reaction was stopped by adding excess soluble chromatin and chilling the reaction on ice. Free TG-151 (F, lane 1) and Nu151 (Nu, lane 11) serve as controls.

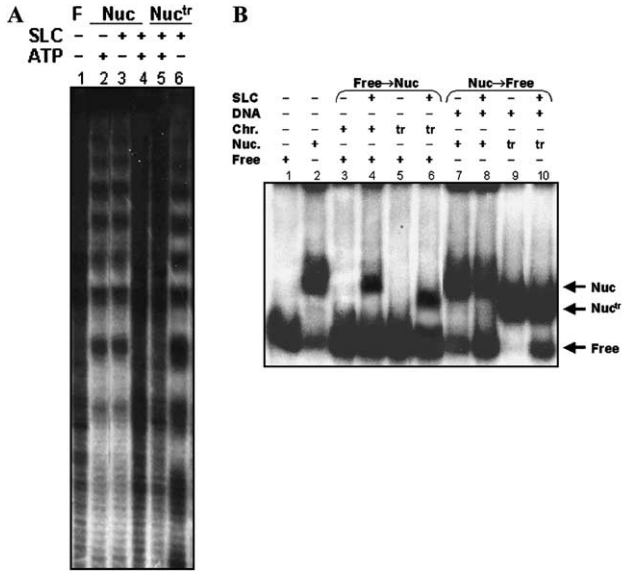

Fig. 5. Remodelling of tailless nucleosomes by SLC. (A) Uniformly labelled tailless nucleosomes (Nuc^{tr}, reconstituted using trypsinized donor chromatin) were treated with SLC and ATP as indicated. Further processing of samples was as mentioned for Fig. 2A. (B) Labelled TG-151 fragments (Free) were treated with ATP and SLC in the presence of native donor chromatin (lanes 3, 4) or trypsinized donor chromatin (tr, lanes 5, 6). Conversely, labelled nucleosomes (native, lanes 7, 8; and tailless: tr, lanes 9, 10) were treated with ATP and SLC in the presence of acceptor DNA. Both native and tailless nucleosomal sources can support octamer transfer reactions. Note that the tailless nucleosomes (Nuc^{tr}) migrate faster than the native ones (Nuc). TG-151 fragment and native Nu151 (lanes 1 and 2, respectively) serve as controls.

nucleosomes, and such nucleosomes will not be drastically unstable. Therefore, titrating the existing nucleosomal DNA by extraneous DNA would not be easy, and would essentially require active participation of a remodelling factor in an ATP-consuming reaction. In vivo, however, such reactions would probably depend upon many factors including (i) whether or not the nucleosome in target encompasses a nucleosome positioning sequence, (ii) 3-dimensional geometry of both the site of action and the remodeller, (iii) availability of free DNA as octamer sink, (iv) modification status of the nucleosomal histones in target, and (v) other regulatory or architectural proteins in proximity. Though unclear how, such an active participation of the remodelling factors in allowing transient exposure of small stretches on nucleosomal DNA, or active transfer of octamers onto nucleosome-free regions would present a profound means of gene regulation.

Acknowledgments

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Note added in proof. While this paper was in review, Kassabov et al. (Mol. Cell 11 (2003) 391–403) reported that reorganization of nucleosomal DNA topology by the yeast SWI/SNF is accomplished within a second. Our results, though of less temporal resolution, are consistent with this finding regarding the rapidity of nucleosome disruption.

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