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Review

Targeting chromatin remodelers: Signals and search mechanisms ☆

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ABSTRACT

Chromatin remodeling complexes are ATP-driven molecular machines that change chromatin structure by translocating nucleosomes along the DNA, evicting nucleosomes, or changing the nucleosomal histone composition. They are highly abundant in the cell and numerous different complexes exist that display distinct activity patterns. Here we review chromatin-associated signals that are recognized by remodelers. It is discussed how these regulate the remodeling reaction via changing the nucleosome substrate/product binding affinity or the catalytic translocation rate. Finally, we address the question of how chromatin remodelers operate in the cell nucleus to find specifically marked nucleosome substrates via a diffusion driven target location mechanism, and estimate the search times of this process. This article is part of a Special Issue entitled:Snf2/Swi2 ATPase structure and function.

1. Chromatin remodeling in mammalian cells

Chromatin remodeling complexes hydrolyze ATP to control nucleosome positioning. They are able to evict nucleosomes and are involved in exchanging canonical core histones with histone variants [1]. Their ability to (re)position nucleosomes plays an important role for regulating gene expression as well as mediating access to the DNA during replication and repair [2–9]. Remodeling complexes typically consist of an ATPase containing motor protein and different accessory proteins [1] (Fig. 1). The ATPase subunits of chromatin remodeling enzymes belong to the SF2 superfamily of helicase-related proteins and contain a common core of two RecA helicase domains [10,11]. These couple ATP hydrolysis to protein conformational changes [12]. Within the SF2 helicase group, most chromatin remodeling enzymes belong to the Snf2 family that can be further divided into several subfamilies [13]. The most prominent ones are SWI/SNF, ISWI, CHD and INO80 [1,13]. However, also proteins from other subfamilies such as the Rad54-like remodeler ATRX appear to play important roles in controlling chromatin organization [14,15]. In addition to the helicase domain, proteins of a given family share other characteristic domains that define their biological functions (Fig. 1A). SWI/SNF members contain a bromodomain, ISWI members contain a HAND-SANT-SLIDE domain, and CHD members contain a double chromodomain. ATPases belonging to the INO80 group are characterized by a "split" helicase, which has a long insertion separating the DExx and HELICc domains [13]. Specific interactions of chromatin remodeling complexes with their modified and unmodified nucleosomal substrates can be established via domains of the ATPase and/or associated subunits (Fig. 1). Interactions with nucleosomes are mediated by the bromodomain (BRD/bromo, acetylated histones), the bromo-associated homology domain (BAH, nucleosomes), the chromodomain (CHD/chromo, methylated histones), the plant homeodomain (PHD, unmodified/acetylated/methylated histone tails, globular domain of histones) or HAND/SANT/SLIDE domains (nucleosomes and nucleosomal DNA) as reviewed previously [1] and discussed in Section 2. While the conserved helicase domains suggest a common remodeling mechanism, the diversity of remodeling complex composition points to a high selectivity with respect to the recognition of specific nucleosomal substrates and to a functional diversity of their activity. Here, we review chromatin-associated signals that are recognized by chromatin remodeling complexes and discuss how these control their activity. The different types of signals and their readout by chromatin remodelers are illustrated for prototypic examples. Furthermore, principles for target search and identification mechanisms of remodelers are discussed.

2. Chromatin binding signals that target chromatin remodelers

In the cell the ATP-dependent activity of chromatin remodeling complexes makes an important contribution to position nucleosomes [2,4,5,7,8]. This involves an active regulation of nucleosome localization in the context of the developmental and metabolic state of the cell via the targeted action of ATP-dependent chromatin remodeling complexes as demonstrated in numerous studies [16–20]. These complexes can read chromatin signals like DNA sequence, structure or methylation, recognize histone modifications, detect the presence of histone variants, and can interact with chromatin-associated proteins such as transcription factors to identify specific target nucleosomes in

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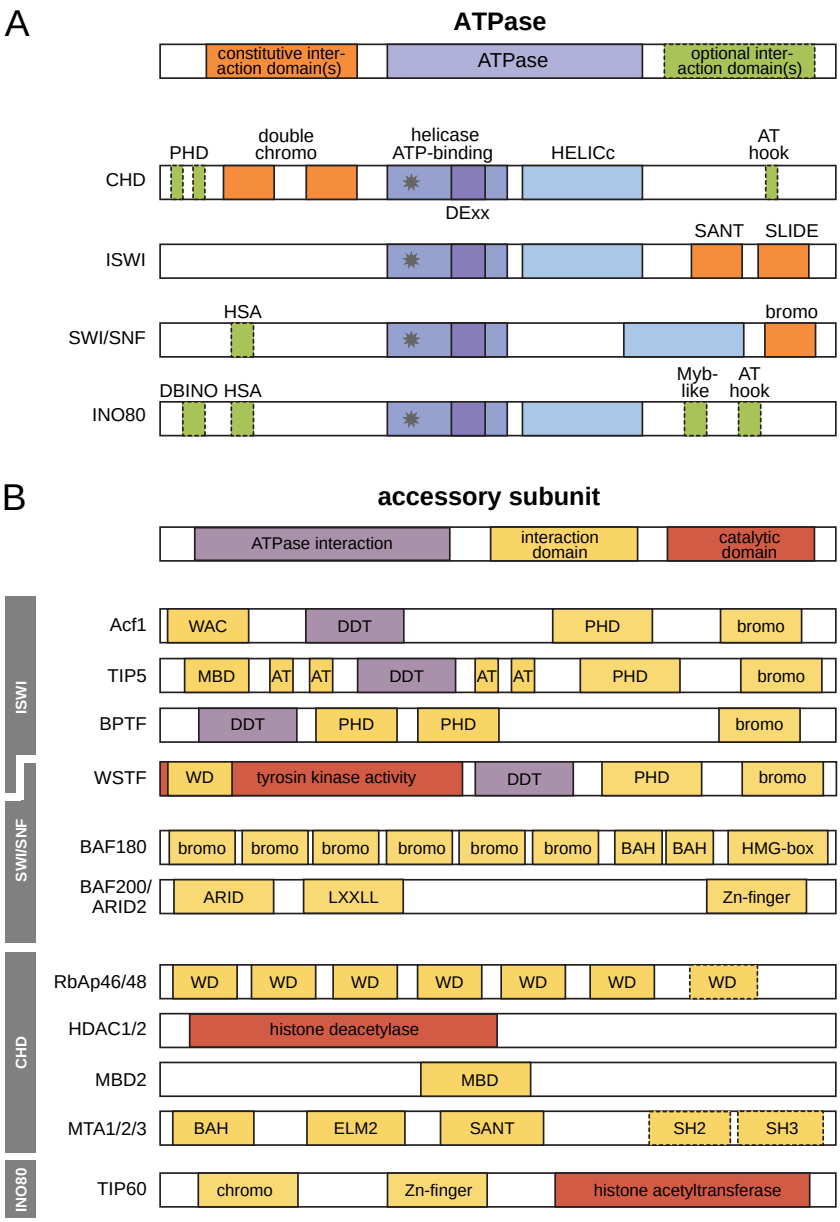

Fig. 1. Protein domain structure of chromatin remodeling complexes. Chromatin remodeling complexes consist of a catalytic ATPase, which belongs to the SF2 helicase superfamily, and accessory regulatory subunits. (A) In the CHD, ISWI and SWI/SNF families the ATPase domain (blue color) is interrupted by only a small protein sequence, whereas the ATPase domain of the INO80 family is "split" by a long insertion. In the scheme the ATP binding site is indicated by a star, the DExx motif is depicted in dark blue and the helicase C terminal domain (HELICc) in light blue. Although the families of ATPases share a common catalytic domain they contain unique flanking regions for interactions with (i) DNA via SLIDE, AT hook (AT), DBINO and possibly Myb-like domains, (ii) chromatin via SANT, bromo- (bromo) or chromodomains (chromo), and (iii) with other proteins as mediated for example by the helicase-SANT-associated (HSA) domain. The interaction domains present in all family members are indicated in orange, while those that are present in only a subset of the family members are colored in green. (B) Noncatalytic subunits of chromatin remodeling complexes can regulate the activity and the substrate recognition of the complex. Via the homeobox and DDT domains they interact with the ATPase domain and bind DNA. DNA interaction modules are also present in MBDs AT hooks (AT), WAC motifs, Zinc fingers, ARID and high mobility group (HMG) domains. Finally, histones or histone modifications are recognized by subunits with bromo, chromo, SANT and PHD motifs while interactions with other proteins or protein modifications are mediated by WD, SH2, SH3 and ELM2 domains or the LXXLL motif. Moreover, some associated proteins contain catalytic activity as for example WSTF, Tip60 and histone deacetylase 1/2 (HDAC1/2). The functions of the bromo-associated homology domain (BAH) are currently unknown.

the nucleus. An additional level of regulation is the alternative splicing of remodeling complex components that results in different isoforms with distinct properties. Splice variants that differ in their chromatin interaction properties and cellular localization have been reported for the BPTF subunit of the NURF complex [21] and the ISWI ATPase Snf2L [22,23]. The best-studied types of nucleic acid and histone signals that have been identified so far are summarized in Table 1. They modulate binding and activity of chromatin remodelers as discussed in the following.

2.1. DNA and RNA

Remodeling complexes contain DNA-binding motifs that are present in the ATPase or in accessory subunits (Fig. 1). Examples are the SLIDE domain in ISWI remodelers or the WAC motifs and AT hooks in Acf1 and TIP5 [1,52–56]. Thus, it is expected that the DNA-binding affinity of remodelers is modulated by the DNA-sequence [2,4,5]. In addition, their nucleosome positioning activity in the cell reflects a complex interplay of numerous factors including the intrinsic DNA

Table 1
Nucleic acid and histone signals recognized by chromatin remodelers.

Signal	Remodeling complex [a]	Comment[b]	Reference
DNA/RNA			
DNA sequence	hACF, yChd1, yRSC, hSWI/SNF, yISW1a/1b/2	nucleosome sliding, enzyme accessibility	[24–28]
DNA quadruplex	h/mATRX	mobility shift	[29]
DNA methylation	hSnf2H/cohesin, x/hNuRD via MBD2	ChIP after 5-azacytidine treatment	[30]
		mobility shift, nucleosome distribution	[31–33]
RNA	h/mNoRC	*in vivo* and *in vitro* binding	[34,35]
Histone modification			
H3K4	hNuRD	pull down, peptide competition	[36]
H3K4me3	d/m/hNURF via BPTF/NURF301	pull down, Co-IP, ChIP, immunofluorescence	[21,37]
H3K4me2/3	y/hChd1	pull down, fluorometric titration	[38]
H3K9me/ac	hChd4 via PHD2 finger	binding by tryptophan fluorescence and NMR	[39]
H4K16ac	m/dNoRC via mTIP5/dNURF301	pull down, ChIP	[21,40]
H4K12/K16ac	dISWI	ATPase competition	[41]
H3ac/H4ac	hSnf2H/cohesin	ChIP	[30]
H3S10p	xISWI	immunoblotting of chromatin bound polypeptides	[42]
H3T118p	ySWI/SNF	nucleosome remodeling	[43]
H2BK120Ub	hSnf2H	ChIP, siRNA	[44]
Core and variant histones			
histone central domain	dACF via PHD finger	nucleosome sliding, pull down, mobility shift	[45]
H2A C-terminus	dACF, dISWI, yRSC, hSnf2H	nucleosome sliding	[46,47]
H2A.Z	hSnf2H/hSnf2L complexes	enzyme accessibility	[48]
H2A.X	m/hWICH, hSWI/SNF	Co-IP, MS, IP, siRNA	[49,50]
H3.3	mATRX with histone chaperone Daxx	Co-IP, MS, fluorescence microscopy	[14,15,51]

[a] Small letters indicate organism.
[b] IP, immunoprecipitation, Co-IP, co-immunoprecipitation, ChIP, chromatin immunoprecipitation, MS, mass spectrometry, NMR, nuclear magnetic resonance spectroscopy.

sequence specificity of nucleosomes as well as the competitive binding of transcription factors and the histone octamer [2–6]. Hence, it is difficult to distinguish the direct and indirect effects of DNA sequence. Nevertheless, it has become clear that the outcome of the remodeling reaction can be changed by the DNA sequence as evident from a number of *in vitro* studies [24–28]. In particular, special conformational features of the DNA could play an important role. This was shown for the ISWI-type complex ACF, which can be directed by an intrinsically curved DNA sequence element [24]. Since a number of subunits of remodeling complexes contain MBD domains capable of recognizing methylated DNA, this modification might also be critical for targeting chromatin remodelers [31–33]. Furthermore, unusual DNA structures like quadruplexes could represent binding signals [29] as well as RNA that has been shown to interact with the NoRC remodeling complex [34]. The DNA-sequence dependent targeting of remodelers is not necessarily mediated by the remodeling complex subunits themselves but can also occur via interactions with other proteins. One example is CHD8 that is brought to its target sites by CTCF in a DNA sequence- and methylation-dependent manner and that is essential for the maintenance of the insulator function at imprinted loci [57]. Other examples reviewed previously are the recruitment of chromatin remodeling complexes to specific genes by nuclear hormone receptors or the binding to DNA damage sites via interactions with proteins of the DNA repair machinery [9,58–61].

2.2. Histone modifications

Distinct histone posttranslational modifications are recognized via dedicated protein domains like bromodomains for acetylated histone tails or chromodomains and PHD fingers that interact with methylated lysines [62]. These interaction domains are present both in several regulatory subunits and the ATPase of chromatin remodeling complexes. RSC, Chd1, ISWI and Acf1 all contain bromodomains that recognize the histone acetylation state to promote or inhibit their activity [41,52,63–65]. With respect to histone methylation it was found that human but not yeast Chd1 binds to H3K4me2/3 stronger than to H3K4me1 via its double chromodomains [38]. Methylated lysine residues on histone H3 tails can also be recognized by PHD fingers in a protein context dependent manner [62]. In BPTF, the main subunit of the NURF complex, the PHD finger has been shown to interact specifically with H3K4me3 [37], whereas the PHD2 finger of Chd4 interacts with histone H3 when lysine 9 is monomethylated, dimethylated or acetylated (H3K9me1/me2/ac) but not when lysine 4 is methylated [39]. The affinity of PHD1 of Chd4 to the H3 tail decreases after methylation and acetylation of H3K4 but in contrast to PHD2 the affinity for unmodified and methylated H3K9 does not change significantly [66]. *In vitro* sliding assays indicate that the PHD finger in Acf1 is necessary for the recognition of the central histone moiety [45] although it is currently unknown if this interaction is modulated by histone modifications.

Finally, chromatin remodelers may directly or indirectly modulate epigenetic patterns via their association with histone modifiers. The NuRD complex for example contains the histone deacetylases HDAC1/2 [67]. Another example is the Snf2H containing complex NoRC, which interacts with Dnmt1/3 and HDAC1/2. Besides the remodeling activity of Snf2H both components are shown to contribute to the silencing of rRNA genes [68]. Moreover, it has recently been demonstrated that the SWI/SNF-like chromatin remodeler SMARCAD1 promotes methylation of histone H3K9 in association with histone deacetylases HDAC1/2 and the histone methyltransferase G9a/GLP [69].

2.3. Histone variants

Chromatin remodeling complexes are involved in the non-replicative incorporation and stabilization of histone variants H3.3 (Chd1 [70] or ATRX [14,15,51]), H2A.Z (Swr1 [71]) and CenH3/CENP-A (Chd1 [72] and RSF [73]). For this process it is difficult to distinguish if the histone variant represents only the product of the remodeler-driven incorporation reaction or whether already incorporated H3.3, H2A.Z or CenH3 recruits additional remodeling complexes to enhance the reaction. For ATRX it has been shown that it incorporates H3.3 into chromatin only at telomeric [14,15,51] or pericentric [74] regions together with the histone chaperone Daxx. Although a complex of ATRX and H3.3 has been isolated by co-immunoprecipitation [14,15,51] it appears that ATRX is associated relatively weakly with H3.3 as compared to the Daxx-H3.3 interaction [14]. Thus, other

targeting factors in addition to H3.3 are likely to be required for the association of ATRX with telomeres and the subsequent non-replicative incorporation of H3.3.

With respect to the control of the nucleosome translocation reaction, histone variants have been identified as signals that change the activity of chromatin remodelers. The histone variant H2A.Z, which is often found in nucleosomes at transcriptional control regions, increases the activity of human ISWI remodeling complex *in vitro* [48]. Since H2A.Z has been linked to both silencing and transcriptional activation, this increase might be related to a function of Snf2H in transcriptional control of the corresponding genes. Another example refers to nucleosomes containing H2A.X, which is important for the maintenance of genome integrity. This variant was shown to bind more strongly to the WICH complex than nucleosomes with canonical H2A [49]. Furthermore, H2A.X is a substrate for the WSTF kinase that is part of the WICH complex. Accordingly, this interaction could be relevant for targeting the WICH complex to DNA repair sites. Histone variants within the H2A family show high divergence in their C-terminal regions. Since interaction with the C-terminal tail also regulates the remodeling reaction as shown for recombinant human Snf2H or *Drosophila* ISWI and ACF as well as RSC [46,47], differences in affinities or translocation rates for the corresponding histone variants are expected.

3. Effects of targeting signals on chromatin remodeling activity

As discussed above, a variety of chromatin signals are recognized by chromatin remodeling complexes and modulate their activity (Table 1, Fig. 2A). To dissect the underlying mechanism, it is instructive to describe the kinetics of the remodeling reaction by a Michaelis–Menten scheme to identify steps that could affect the reaction (Fig. 2B). According to the scheme depicted in Fig. 2B the remodeling reaction is decomposed into the following steps: (i) The reaction is initiated with the binding of a remodeler to a nucleosome. The efficiency of this reaction is determined by the remodeler concentration and the equilibrium binding constant to the initial nucleosome substrate, i.e. the ratio of $k_{on,start}/k_{off,start}$. (ii) The translocation reaction is initiated with rate k_f and involves the formation of a high-energy intermediate. This could be for example the dissociation or loop formation of DNA at the site where it enters/exits the nucleosome. This reaction may represent a proof reading step as proposed previously [75]. It would involve ATP hydrolysis and the unproductive decay of this intermediate into remodeler and initial nucleosome substrate with rate $k_{release}$. (iii) The translocation reaction proceeds with rate k_{cat}. (iv) Finally, the remodeler terminates the translocation reaction by dissociation from the nucleosome, with an efficiency that depends on $k_{on,end}/k_{off,end}$.

The remodeling reaction bears some similarity to the events that occur during transcription in *Escherichia coli*, which have been studied extensively [76–79]. The essential and rate limiting steps of this process are (i) the binding of RNA polymerase (RNAP) holoenzyme to the promoter, (ii) DNA duplex strand separation at the promoter, i.e. open complex formation as a high-energy intermediate (iii) promoter clearance and transition into a stable elongation phase or abortive RNA synthesis of short fragments, (iv) elongation, which itself can be further regulated by RNAP pausing, backtracking, etc., and (v) termination. For *E. coli* transcription the following observations were made. With respect to the "strength" of *E. coli* promoters to initiate transcription two classes of initiation events were identified. In the first class, the initiation reaction was limited by the binding affinity of RNAP. The second class showed a high binding affinity because of a lower k_{off} but a slow conversion rate k_f into the open complex [76]. After successful initiation, the rate of elongation can be modulated by sequences that pause the elongating RNAP at certain sites [77,80]. Finally, termination can be induced by sequences that reduce the affinity of RNAP to the template and thus promote its dissociation [78,79]. In comparison, we propose that chromatin associated signals can affect the corresponding four steps of the chromatin remodeling reaction: (i) the remodeler binding affinity to the initial substrate, i.e. the equilibrium binding constant $K_{eq,start}$ that equals $k_{on,start}/k_{off,start}$, (ii) the initiation rate k_f with which the high-energy intermediate is

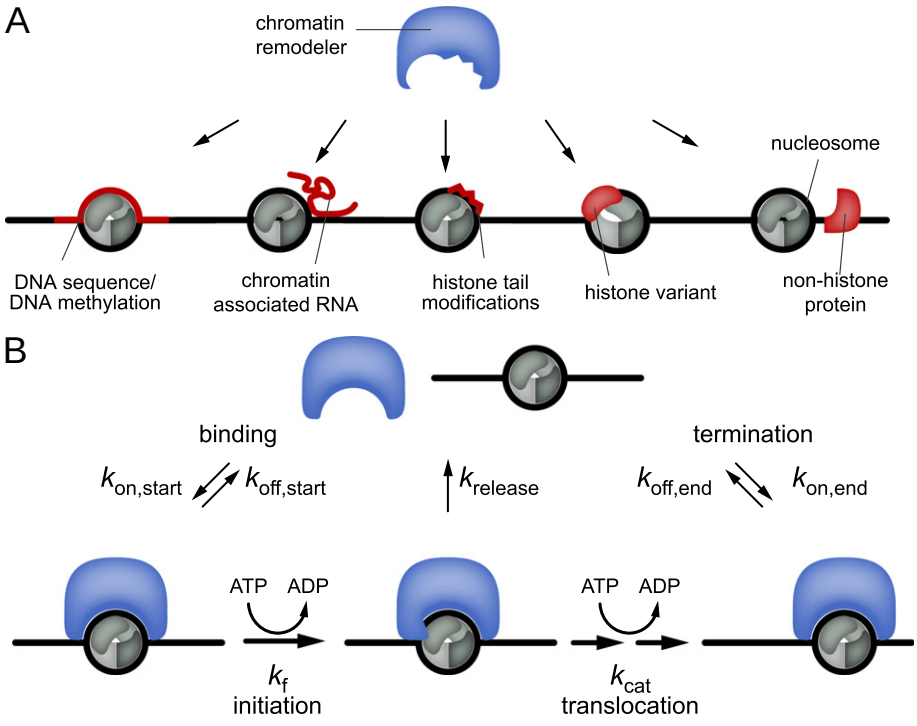

Fig. 2. Target location signals and translocation reaction scheme for chromatin remodelers. (A) DNA, RNA, posttranslationally modified histone tails, histone variants or other chromatin-associated proteins represent chromatin signals that can target chromatin remodelers. (B) Reaction pathway for the nucleosome translocation reaction. As discussed in the text several of the indicated reactions could be subject to regulation via the chromatin associated signals shown in panel A.

formed, (iii) the catalytic translocation rate k_{cat}, and (iv) a reduced equilibrium binding affinity $K_{eq,end}$ to terminate the translocation reaction at a certain position as discussed previously [24]. Thus, as for other enzymatic reactions, chromatin remodeling could be modulated by the initial/terminal equilibrium binding affinity $K_{eq,start}$ or $K_{eq,end}$ to the nucleosome substrate/product or the kinetic rates of initiation and translocation, i.e. k_f and k_{cat}. Examples for both cases are discussed below.

How to integrate this type of mechanistic models into descriptions of large-scale nucleosome position maps is yet another important question in the understanding of how chromatin remodelers operate in a genome-wide context, where the presence of neighboring nucleosomes imposes additional constraints. The first study on this subject devised a generally applicable approach to compute nucleosome position maps iteratively for a certain genomic locus until a new steady state was reached [81]. Chromatin was represented by a one-dimensional DNA lattice with bound histone octamers, and the chromatin-remodeling activity was introduced via a DNA position-dependent probability to translocate the nucleosome. This function was chosen to mimic different types of chromatin remodeling activities to equally space, enrich or deplete nucleosomes. More recently, another study addressed similar issues by using continuous time stochastic simulations of nucleosomes on a DNA lattice [82]. The authors concluded that active histone octamer removal would be a crucial remodeling event for efficient nucleosome repositioning and necessary to establish the high nucleosome density observed *in vivo*.

3.1. Chromatin signals that influence the binding affinity to the nucleosome substrate

Nucleosome-associated signals can determine the affinity between the nucleosome and a chromatin remodeler. Initial targeting of the remodeler to a specific nucleosome substrate can be achieved by increasing the binding affinity via posttranslational modifications. Chd4 for example discriminates between different modification patterns of the H3 tail. Its PHD2 finger has a higher affinity to the methylated or acetylated state of lysine 9 of histone H3 as compared to the unmodified tail, whereas methylation of lysine 4 decreases its binding affinity [39]. A recent NMR study revealed that H3K4 binds to a canonical pocket, whereas the H3K9 residue interacts with a phenylalanine residue on the surface [66]. Human Chd1 in contrary binds to methylated H3K4, which requires both of its chromodomains. *In vitro* binding studies showed that Chd1 recognizes monomethylated H3K4 with a 3-fold lower affinity than di- and trimethylated H3K4 [38]. The RSC complex interacts with acetylated H3K14 via its tandem bromodomain [83]. Enzyme kinetic measurements revealed that the binding of RSC to histone H3 is increased upon tetra-acetylation of the N-terminal tail as well as single acetylation of H3K14, whereas the catalytic turn over rate remained unaffected [65]. In *Drosophila*, increased H4K12/H4K16 acetylation reduced binding of ISWI since it interfered with the binding of the SANT domain to H4 tails [52]. This lead to ISWI dependent changes in chromatin structure and an enhanced gene expression [41]. Thus, a change of the H3 or H4 modification state could represent a signal that marks a nucleosome for translocation by increasing the binding affinity to a certain type of remodeling complex. This type of interaction is unlikely to depend on the nucleosome position. In contrast, interactions of the remodeler and nucleosomal and/or linker DNA can change between the initial nucleosome substrate and the reaction end product inasmuch as they are DNA sequence dependent. This would provide a mechanism to direct the translocation reaction to certain sites as proposed previously based on binding affinity measurements of Chd1 and ACF [24].

3.2. Chromatin signals that affect the catalytic rate of chromatin remodelers

The efficiency of the remodeling reaction can be regulated not only by the initial binding step but also by the catalytic rate constant, i.e. the velocity of the remodeling reaction as given by k_f and k_{cat} in Fig. 2B. A change of the catalytic activity has been observed for different chromatin remodelers depending on the type of nucleosome modification. The ISWI ATPase for example contains a SANT domain, which can interact with the unmodified tail of histone H4. In the absence of this interaction, i.e. upon deletion of the H4 N-terminus, remodeling and ATPase activity of ISWI are abolished [84,85]. Furthermore, as mentioned above, the mammalian ISWI complexes display an increased translocation rate under saturating conditions with H2A.Z-containing nucleosomes as compared to nucleosomes with canonical H2A [48]. This suggests that the catalytic rate of ISWI proteins is sensitive to the presence of this histone variant in its nucleosome substrate. Histone H4 lacking its N-Terminal tail was found to reduce the catalytic turnover rate of Chd1 (and Isw2) remodeling enzymes without affecting recruitment in yeast [65]. The crystal structure analysis of Chd1 revealed that the double chromodomain of Chd1 negatively regulates the ATPase activity [86]. Interaction with a nucleosome relieves this inhibition and promotes remodeling. Thus, the Chd1 chromodomain contributes to the discrimination between naked and nucleosomal DNA by reducing the ATPase activity on naked DNA.

4. Targets of chromatin remodelers in the nucleus

For the discussion of target search mechanisms of chromatin remodelers it is instructive to consider two scenarios. One is the accumulation of remodelers at replication foci or repair sites that have typical sizes in the range of 50–200 nm [87–89]. Interestingly, this process is associated with the binding of many different types of chromatin remodeling complexes. The other case is the targeting of a chromatin remodeler to a certain genomic locus like a promoter of a specific gene as it occurs in differentiated cells in response to an environmental stimulus or upon cell lineage commitment of embryonic stem cells. In the latter case, the gene expression pattern is changed for many genes simultaneously. In general, gene-specific transcriptional regulation can be assigned to a certain type of remodeling complex. These complexes need to identify a specific nucleosome, i.e. a cylindrically shaped target with dimensions of 5.5 nm height and 11 nm diameter, in a human diploid cell nucleus containing ~30 million nucleosomes. This process has to occur sufficiently fast to be compatible with typical cellular response times on the time scale of minutes.

4.1. Large scale accumulation of chromatin remodelers during DNA replication/repair

Both in the case of DNA replication and DNA repair, spherical nuclear subcompartments of 50–200 nm in diameter are assembled containing numerous proteins. In both cases, chromatin remodeling is required to make the DNA accessible for effector proteins, such as polymerases, and to reestablish the proper chromatin structure after replication or repair has finished. Among the factors recruited to replication foci and DNA damage sites are chromatin remodelers from all families. At replication foci, the SWI/SNF remodeler Brg1 [90], the ISWI complexes ACF [91] and WICH [92], as well as the INO80 complex [93] were found with different functions. Brg1 accelerates replication elongation, possibly by facilitating the removal of nucleosomes downstream of the replication fork. In contrast, WICH is responsible for the assembly of newly synthesized DNA into chromatin. ACF, which shares the Snf2H motor protein with the WICH complex, plays a role in replication of heterochromatin in later stages of S phase. At damage sites, the SWI/SNF ATPase Brg1 [94], the ISWI complexes WICH [49] and ACF/CHRAC [9,95], the CHD remodeler Chd4 [96,97], the INO80 complex [98], the p400 ATPase [99] as well as SMARCAL1 [100] have been detected. Besides nucleosome translocation, many of these remodelers also have functions in recruiting additional factors to the

replication focus/damage site or in covalently modifying histone tails [49,50].

4.2. Gene specific regulation via nucleosome repositioning

4.2.1. Transcription regulation by chromatin remodelers in differentiated cells

Chromatin remodelers can change gene expression levels via nucleosome repositioning at specific promoters in response to hormone-dependent stimulation or metabolic changes as reviewed previously [5,61,101]. A prototypic example for the complex interplay of various chromatin signals associated with switching nucleosome positions during repression/activation is the transcription of ribosomal genes by RNA polymerase I. It is assumed that on silent ribosomal DNA (rDNA) promoters the nucleosome covers the sequence of the core ribosomal promoter element, whereas the binding sites for the transcription factor UBF and a CpG island are placed within the linker region. Thus, the promoter is locked for transcription initiation. On active promoters the regulatory nucleosome is oriented such that the core element of the rDNA promoter is accessible and juxtaposed to the UBF binding site on the linker DNA enabling transcription initiation [68,102,103]. The switching between both conformations is mediated by distinct chromatin remodeling complexes. The NoRC complex, composed of Snf2H and TIP5, acts as a repressor of rRNA transcription [55,104]. NoRC can be recruited to the rDNA promoter by its interaction with the transcription termination factor TTF-I [105], its binding to H4K16ac by the bromodomain of TIP5 [40] and by its interaction with a promoter complementary transcript [34]. It shifts the promoter-bound nucleosome into the silent position [103]. In addition to this activity, NoRC recruits epigenetic modifiers like the histone deacetylase HDAC1 and DNA methyltransferases to silence transcription [68]. The putative counterpart of NoRC that establishes the nucleosome position of the active state at the rDNA promoter is B-WICH, which consists of the WSTF-Snf2H complex WICH and nuclear myosin [106,107].

4.2.2. Control of cell differentiation by chromatin remodelers

During cell differentiation, a number of chromatin remodelers are involved in activating or repressing specific sets of genes, which are relevant for development. Chd1 [108], NURF [109], NuRD [110–112], the Tip60-p400 [113] and the esBAF complex [113,114] are essential for both maintaining pluripotency and changing the gene expression pattern during cell differentiation [17]. Recent studies indicate that differential expression and alternative splicing of remodelers as well as the recognition of histone modifications and histone variants contribute to targeting of chromatin remodeling complexes to certain sites during cell lineage commitment. Many genomic regions in embryonic stem cells (ESCs) show a characteristic pattern of DNA-methylation, histone modifications and histone variants. Chromatin is globally hyperacetylated at histones H3 and H4 [115] and several loci show active H3K4me3 as well as repressive H3K27me3 marks [116]. It is noted that two Snf2L complexes containing the BPTF (NURF) or CECR2 subunit (CERF) as well as Chd1 recognize the H3K4 methylation status. Thus, it appears likely that this is also a signal to modulate their activity during differentiation. BPTF, the large subunit of NURF is essential for mouse embryonic development. It was shown to bind H3K4me3 by its PHD finger and to regulate the expression of the developmental genes engrailed and Hoxc8 [37,109,117]. In *Drosophila* alternative splicing of NURF301/BPTF creates an isoform without the C-terminal PHD finger/bromodomain, deficient in H3K4me3 and H4K16ac recognition with an accordingly different function in development [21], suggesting the importance of recruitment signals for differentiation. Another way to specifically recruit developmentally relevant remodeling complexes is the interaction with transcription factors. This was shown for NURF, which binds to Smad, a component of various signaling cascades [109].

Knockdown of the chromatin remodeler Chd1 in ESCs induces neuronal differentiation, and inhibits reprogramming of fibroblasts [108]. Chd1 is known to mediate an open chromatin state. Its knockdown decreases Oct4 promoter activity and enhances formation of additional heterochromatin foci with methylated H3K9 and HP1 marks. Surprisingly, most genes of neurogenesis became upregulated in Chd1 knockdown cells arguing against a general activating function [108]. How Chd1 specifically regulates genes of pluripotency and differentiation remains elusive, but it is tempting to speculate that the previously demonstrated ability to recognize H3K4me2/H3K4me3 via its double chromodomains plays a role in this process [38].

In developing neuronal cells, subunit exchanges can regulate the specificity of BAF complexes. These complexes consist of the interchangeable ATPase subunits Brg/Brm and eleven tightly associated core subunits [118,119]. Brg-containing BAF complexes regulate the expression of components of the Notch and the Hedgehog signaling pathways and thus control neural stem cell self-renewal and proliferation. The subunits BAF45a and BAF53a are expressed in proliferating neuronal progenitors, whereas BAF45b, BAF45c and BAF53b are predominantly present in post-mitotic neurons [118]. Preventing subunit switching was shown to impair neuronal differentiation [118]. Thus, BAF45a but not the homologous BAF45b subunit is sufficient to enhance neural stem/progenitor cell proliferation. The C-terminal region of BAF45, which is mainly conserved between both isoforms, contains a double PHD finger domain (43% identity and 63% similarity of amino acids) whereas the less conserved N-terminal region comprises a C_2H_2-type Krüppel-like zinc finger domain. Analysis of BAF45a deletion mutants specifies the N-terminal region as well as the Krüppel-like domain to be essential for neural stem/progenitor cell proliferation [17]. The Krüppel-like domain is a zinc finger domain that could provide DNA sequence specific interactions as observed in various transcription factors but its role in recruiting BAF complexes to certain genes remains to be investigated.

5. Search and find mechanisms of chromatin remodelers in the nucleus

As discussed above there is a large variety of chromatin-associated signals that are recognized by different chromatin remodeling complexes and affect their remodeling activity. These signals can operate via changing either the nucleosome binding affinity or the catalytic rate with which the histone octamer is translocated (Fig. 2B). From the considerations made above it is apparent that for localized gene-specific regulation, single nucleosome positions need to be controlled via the readout of chromatin signals that can change in response to certain stimuli. Accordingly, histone modifications are dynamically set and removed by histone methyl- and acetyltransferases [120]. This scenario imposes the requirement for chromatin remodelers to continuously probe essentially all nucleosomes of the genome with respect to the associated signals that could mark them for translocation. This process needs to operate on the time scale of minutes, in which a cell is able to respond to external stimuli. How can this be achieved? According to the kinetic scheme depicted in Fig. 2B the rate $k_{on,start}$ for the initial binding of the remodeler to its correct target nucleosome is rate limiting if it is significantly lower than the rates of the subsequent reactions. This reaction would include all steps preceding the first ATP-dependent reaction. These could involve conformational rearrangements that are associated with a significant activation free energy barrier as for example an ATP hydrolysis-independent unwrapping of DNA [121] or the formation of a closed, ATP hydrolysis-competent conformation [86]. The formation of these intermediates could contribute significantly to the resulting binding rate but a further decomposition of $k_{on,start}$ into distinct steps is not considered here. It is noted that the value of $k_{on,start}$ might critically depend on the specific type of nucleosome substrate, i.e. target nucleosomes for a given type of remodeling complex versus

nucleosomes that are transiently bound but not translocated. As discussed in the following the value of $k_{on,start}$ appears to be indeed low in the nucleus. Remodelers need to find a small and essentially immobile chromatin target represented by a DNA replication/repair site or a particular nucleosome in an environment that is highly concentrated with proteins and nucleic acids. These macromolecules affect the remodeler's mobility and represent a high excess of unspecific binding sites among which the remodeler needs to find the correct one. The search process is random and diffusion driven. Diffusion is a non-energy consuming protein transport process, for which the particle mobility is described by the diffusion coefficient D [122]. On the 10 μm length scale of the nucleus diffusion leads to fast translocations, and an inert particle of the size of a chromatin remodeling complex would take only ~10 s to fully traverse the nucleus. However, the challenge faced by the remodeler is not simply to roam around quickly in the nucleus but to identify its target site on chromatin. In the following, the general concept of diffusion-driven target location by chromatin remodelers is outlined, and the critical parameters that determine the efficiency of the nucleosome search process in the cell nucleus are discussed.

5.1. Target search by free three-dimensional diffusion

The driving force of diffusion is random collisions with surrounding particles. Whereas a protein in a diluted aqueous solution collides predominantly with water molecules, its mobility in the crowded environment of the cell nucleus is additionally affected by collisions with macromolecules. In particular, the chromatin network of nucleosome chains acts as immobile obstacles that impede diffusive translocations as will be discussed in further detail in Section 5.3. On the other hand, collisions with chromatin are necessary to identify the binding target. Considering the search for a single immobile nucleosome of radius $r_T = 4$ nm (approximated by a sphere) carried out by a remodeling complex with radius $r_R = 5$ nm and a free diffusion coefficient $D = 70\ \mu m^2\ s^{-1}$ it is straightforward to calculate the collision frequency as the diffusion-limited association rate from Eq. (1) [122].

$$k_{on} = 4\pi D(r_R + r_T)N_A \quad (1)$$

Here, N_A is the Avogadro constant. If the radii are measured in units of dm and the diffusion coefficient in units of $dm^2\ s^{-1}$ the association rate in $M^{-1}\ s^{-1}$ is obtained. For the values specified above, $k_{on} \approx 10^9\ M^{-1}\ s^{-1}$. For larger targets with $r_T = 100$ nm, which corresponds to the size of DNA replication/repair foci, this value increases to $k_{on} \approx 10^{10}\ M^{-1}\ s^{-1}$, i.e. these sites are found 10-fold faster than single nucleosomes. However, due to the sterical requirement of aligning the interaction surfaces of remodeler and nucleosome in the correct manner and possible activation free energy barriers associated with the binding step not every collision will be productive in terms of complex formation [122]. In fact, typical values of k_{on} for the *in vitro* binding of a transcription factor to a short DNA fragment with the binding site are in the range of 10^4 to $10^7\ M^{-1}\ s^{-1}$ as opposed to the diffusion limited rate of ~$10^8\ M^{-1}\ s^{-1}$ [123]. Furthermore, a certain residence time t_{res} might be required for target identification, i.e. a transient binding reaction potentially coupled to a conformational change or a proof reading step as represented by the rate k_f in Fig. 2B. Thus, target identification might represent the rate-limiting step in the nucleosome translocation reaction. It will depend on the probability with which diffusional encounters lead to correctly aligned complexes, the target nucleosome density and the activation free energy barrier to proceed to a translocation competent state. The residence time t_{res} can be estimated from mobility measurements and appears to be on the millisecond time scale for human ISWI remodelers [124]. Transient binding reduces the collision rate and Eq. (1) has to be modified accordingly [122].

For large concentrations c_T of potential targets that have to be transiently bound, the search process can be treated as a first-order reaction that is characterized by the pseudo-association rate $k^*_{on} = k_{on}\, c_T$ which leads to Eq. (2).

$$\frac{1}{k^*_{on}} = \frac{1}{k_{on}c_T} = \frac{1}{4\pi D(r_R + r_T)N_A c_T} + t_{res} \quad (2)$$

The inverse pseudo-association rate corresponds to the time in which the searching protein is free between two binding events at potential target sites. Large target concentrations are typical for search processes where all nucleosomes or all linker DNA sequences in the whole genome have to be at least transiently bound. For a target concentration of 140 μM, which corresponds to the average nucleosome concentration in mammalian cells [125], the diffusion-limited pseudo-association rate for a protein with $D = 70\ \mu m^2\ s^{-1}$ and an interaction radius of 10 nm amounts to roughly $10^6\ s^{-1}$. In practice, this value can be greatly reduced due to orientation constraints and transient binding interactions with potential target sites. As discussed previously, transient binding can be accounted for by replacing D with an apparent diffusion coefficient D_{eff} that is decreased because the particle is trapped part of the time [126]. The fraction of molecules in the bound state is related to the pseudo-equilibrium constant $K^*_{eq} = k^*_{on}/k_{off} = k_{on}\, c_T/k_{off}$, which includes the concentration of free potential binding sites c_T in addition to the kinetic on and off rates. Here, k_{off} is an effective dissociation rate that depends on $k_{off,\ start}$ and $k_{release}$. If both productive and unproductive binding events are transient, k_{off} will correspond to their weighted average; otherwise, k_{off} represents unproductive binding only. The free mobility of the particle described by its diffusion coefficient D is related to its binding properties averaged over all binding sites according to $D_{eff} = D/(1 + k^*_{on}/k_{off})$. Such a behavior is indeed observed for ISWI-type chromatin remodeling complexes for which values of $D_{eff} \sim 1\ \mu m^2\ s^{-1}$ have been measured [124]. Finally, the searching chromatin remodeler picks its nucleosomes randomly, i.e. without a preferred order. Accordingly, a considerable redundancy of remodeler–nucleosome interactions is required to probe all possible binding sites. If the search process is divided into a sequence of association–dissociation cycles, the number of new targets that are bound in each cycle decreases drastically with the cycle number [124]. This leads to an inefficient search if every single target has to be probed. For example, if a remodeler like Snf2H would need 40 s to probe 90% of all nucleosomes, it would need 80 s to probe 99% and 120 s to probe 99.9% of all nucleosomes.

In summary, $k_{on,start}$ and the corresponding search time of a remodeler to find its specific nucleosome substrate are slowed down by the following contributions: (i) Remodeler–nucleosome complexes are formed only in a small fraction of diffusive collisions. (ii) A certain residence time t_{res} might be required for target identification. (iii) The transient binding to "wrong" sites reduces the freely mobile fraction. (iv) For complete coverage of all nucleosomes via a random search an increasing number of nucleosomes has to be tested multiple times. The combination of the above effects could make the search time prohibitively long, which warrants some additional considerations on other factors that could contribute to the search time in the nucleus.

5.2. Reduction of dimensionality

Some proteins and possibly also chromatin remodelers have the ability to diffuse along the DNA chain or the chromatin fiber [123,127–129]. In contrast to three-dimensional diffusion, movement along the chromatin fiber ensures that every nucleosome or DNA segment along the fiber is encountered. If a protein changes between three-dimensional (3D) and one-dimensional (1D) diffusion, the corresponding search process can be divided into sequential cycles similarly to the association–dissociation case discussed above. Within each association–dissociation cycle, the fraction of nucleosomes visited is c_R/c_N [124] (with c_R representing the remodeler concentration and c_N the nucleosome concentration). In contrast, mc_R/c_N is the

fraction of nucleosomes that are sampled in a 1D–3D diffusion cycle if m nucleosomes are probed during the 1D diffusion period. Thus, the fraction of sampled nucleosomes after n cycles can be written as

$$p_n = 1-\left(1-\frac{mc_R}{c_N}\right)^n \quad (3)$$

It implies that no correlations between 1D and 3D diffusion phases exist and that 1D-diffusion trajectories do not overlap, which is justified for relatively short 1D-diffusion periods and an excess of potential targets/nucleosomes. By inspection of Eq. (3) it becomes apparent that the 1D-diffusion periods lead to an effective increase in the remodeler concentration by a factor of m. However, at the same time the cycle length increases at least by a factor of m compared to the association–dissociation case, because the remodeler spends a certain time sliding along the chromatin fiber. If the 1D diffusion coefficient is smaller than the 3D diffusion coefficient, the cycle length is increased even stronger. For a remodeler concentration $c_R = 1$ μM and a nucleosome concentration $c_N = 140$ μM, 642 cycles are required to probe 99% of all nucleosomes by association–dissociation reactions and 62 cycles are required to probe the same number of nucleosomes by 1D–3D cycles with $m = 10$ (according to Eq. (3)). Thus, for this setting the search speed would not be increased by intermittent periods of 1D diffusion. Here, the same pseudo-association rate was assumed for the 3D and 1D diffusion processes. This seems to be justified since the average internucleosomal distance in the nucleus corresponds roughly to the length of the linker DNA (assuming equally distributed nucleosomes at 140 μM concentration). Thus, the distance between neighboring nucleosomes on the same chromatin fiber and that of neighboring nucleosomes on different chromatin fibers are expected to be similar (Fig. 3). The fact that 1D diffusion does not necessarily accelerate search processes is consistent with other reports [130]. Based on the mobility data for ISWI chromatin remodelers given above a one-dimensional diffusion driven search mechanism is not expected to accelerate target search. However, in an *in vitro* experiment with isolated chromatin fibers at low concentration 1D diffusion could be important (Fig. 3).

5.3. Anomalous diffusion

Diffusion in the crowded environment of the nucleus deviates from free diffusion in dilute solution and is generally referred to as anomalous diffusion [131]. In this case the volume searched by a protein increases more slowly with time than in the case of free diffusion. This is due to collisions and interactions with immobile obstacles, such as chromatin (Fig. 3D). For a search trajectory of a chromatin remodeler with multiple transient binding reactions, the anomaly during the intervening diffusion periods can have several effects. On the one hand, crowding could increase the pseudo-association rate, leading to a shorter time between two binding events. This result has been obtained by simulating a particle searching its target on a lattice [132]. On the other hand, restriction of the visited volume leads to a "more thorough" local search, whereas location of distant targets is slowed down. Thus, modulation of protein mobility and crowding in different cellular subcompartments could define regions of more or less thorough searching. The relevance of such a mechanism in living cells remains to be further investigated.

5.4. Chromatin remodeler concentration

A central parameter for assessing the search time of a given chromatin remodeling complex is the concentration at which it is present in the nucleus. While the search time of a remodeler present at 1000 molecules in the nucleus might be prohibitively long to work

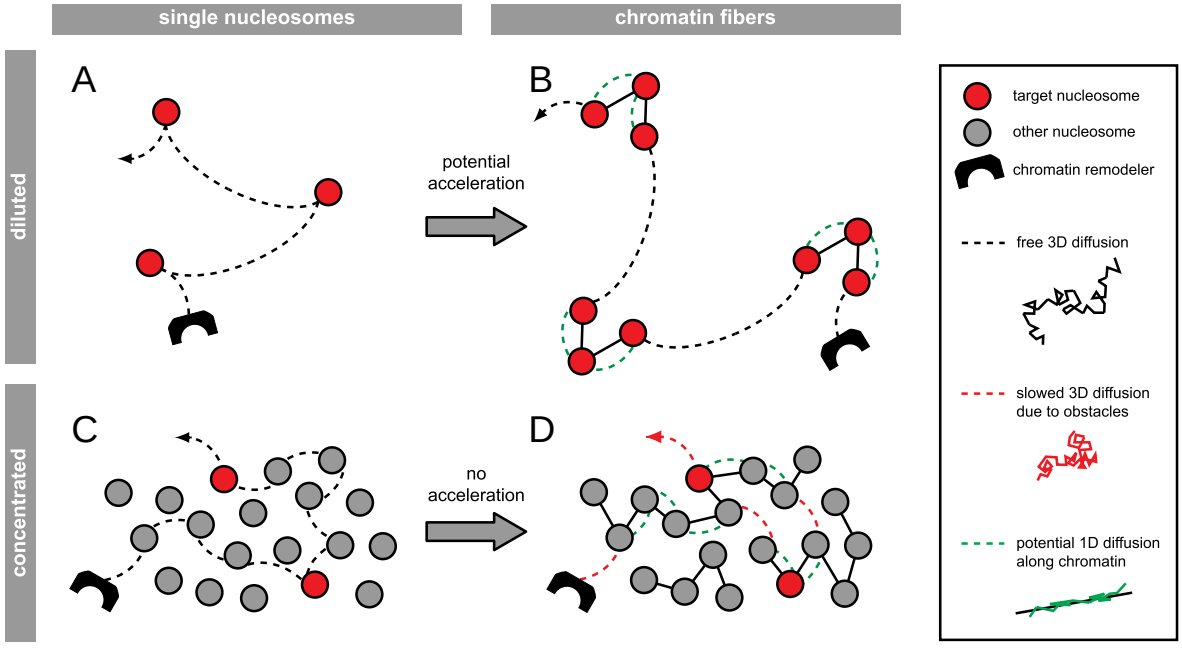

Fig. 3. Diffusion driven target search of chromatin remodelers. (A) In a diluted solution of mononucleosomes, the remodeler diffuses freely and binds its substrate upon productive collision. Typically, in such an experiment the nucleosome population is homogeneous and all nucleosomes represent targets. (B) In a diluted solution of chromatin fibers, the remodeler could potentially move along the fiber part of the time by one-dimensional (1D) diffusion. Compared to panel A, this could accelerate the search process if 1D-diffusion is fast enough. (C) In a concentrated solution of mononucleosomes, the remodeler's substrate interaction mechanism is the same as in a diluted solution (panel A) but the collision frequency is increased due to the larger substrate concentration. (D) In a concentrated solution of chromatin fibers, which represents the situation in the cell nucleus, the remodeler has the option to diffuse between nucleosomes through 3D space (as in panel C) or to move along the chromatin fiber part of the time. Due to collisions or transient binding interactions with the immobile polymer network 3D diffusion is slowed down. As discussed in the text, transient binding leads to a reduced effective diffusion coefficient, while collisions and trapping make diffusion anomalous, i.e. the mean squared particle displacement does no longer increase linearly with time. Since the distance between neighboring nucleosomes in 3D and the distance between neighboring nucleosomes on the same chromatin fiber are similar, 1D diffusion would not accelerate the search process significantly (compare trajectories in panels C and D).

in the cell, one way to speed up the target search could simply be to increase the concentration 100-fold. In general, chromatin remodeling complexes appear to make use of this strategy since they are highly abundant. However, the amount of a specific type of complex may be highly variable depending on cell or tissue type and may be subject to cell type-specific splicing. For example, in humans Snf2H is predominantly found in proliferating cell populations, while Snf2L is enriched in terminally differentiated neurons [133]. Furthermore, Snf2L is expressed ubiquitously but the concentration of its active form is regulated by alternative splicing. The insertion of the non-conserved in-frame exon 13 leads to the catalytically inactive variant Snf2L + 13, which is abundant in non-neuronal tissues. In contrast, the expression of active Snf2L is restricted to neurons and few other tissues [22].

In yeast one remodeler per ~10 nucleosomes is present [134–136], while the number of specific complexes can be highly variable. For example, the RSC complex (1 MDa in size) is present at about 1000–2000 molecules in a haploid yeast nucleus of about 2.9 μm^3 volume. This corresponds to a concentration of ~1 μM or ~1/40 nucleosomes, which is almost 10 times more than the 2 MDa SWI/SNF complex (220 molecules, 0.12 μM, 1/340 nucleosomes) [137]. The variable concentrations of the different groups of remodeling complexes in yeast might correlate with different functional requirements like nucleosome translocation, nucleosome ejection, or histone exchange [136]. Using a combination of fluorescence correlation spectroscopy (FCS) and quantitative western blots remodeler concentrations of 0.83 ± 0.13 μM were determined for endogenous Snf2H in the human U2OS osteosarcoma cell line [124]. This corresponds to about 200,000 Snf2H protein molecules in the nucleus. Extrapolating this value to the total concentration of all remodeling complexes and including complexes of the other ATPase families the total chromatin remodeler concentration in the human cell nucleus is estimated to be in the 10 μM range as compared to a nucleosome concentration of 140 μM [125]. In the same study concentrations >0.15 ± 0.03 μM (hACF complex formed by Snf2H and Acf1), < 0.05 μM (Snf2L) and 0.14 ± 0.04 μM (Snf2L + 13) were determined in the human osteosarcoma cell line.

5.5. Search mechanisms of chromatin remodelers in living cells

Recently, we analyzed the mobility of the ISWI remodelers Snf2H/Snf2L in living cells using fluorescence microscopy based bleaching and correlation techniques [9,124]. These experiments revealed that all ISWI type remodelers were rather mobile in the nucleus during G1/2 phase, and bound only transiently to chromatin with residence times in the 100 ms range. The fraction of remodelers that was bound long enough to catalyze translocation reactions was found to be around only a few percent. However, at replication foci during S phase or at DNA repair sites this fraction of tightly bound remodelers was increased up to 40–70%. Since such an increase was also observed for catalytically inactive Snf2L + 13, binding to these sites occurred also independently of ATPase activity.

In the light of the above considerations a combination of high protein concentrations, short residence times in the chromatin bound state and fast 3D diffusive translocations in the intervening periods appears to be an efficient search and find strategy in the nucleus. Accordingly, we proposed previously that such a "continuous sampling" mechanism for target location applies for ISWI type chromatin remodelers [9,124]. From the experimentally determined relatively high μM nuclear protein concentrations and short chromatin bound residence times around 100 ms, average sampling times of tens of seconds to minutes were calculated for Snf2H containing remodelers to probe 99% of all genomic nucleosomes. Thus, upon the appearance of a trigger signal a nucleosome translocation reaction can be initiated rapidly. This fast target location was confirmed in experiments where the kinetics of chromatin remodeler assembly at DNA repair sites was studied [9]. While the 96–97% mobile fraction of ISWI remodelers is probably not engaged in chromatin remodeling under "housekeeping" conditions in G1/2 phase and is highly mobile in the nucleus they accumulate fast at replication foci during S phase or at DNA repair sites. At these sites a large remodeler fraction is immobilized for seconds to minutes [124]. It is noted that these features of the continuous sampling mechanism are similar to the behavior reported for SWI/SNF and NuRD complexes and a number of transcription factors [138–140].

6. Conclusions

Chromatin remodelers play important roles in many aspects of cell metabolism and development. They are required for DNA replication and repair as well as for transcriptional control upon a variety of stimuli. Whereas the catalytic activity of chromatin remodelers has been characterized in detail *in vitro*, studies addressing their regulation and targeting behavior in living cells appeared only recently. An emerging key question is how remodelers are targeted to sites that require their activity. Here, we have summarized findings on the different layers of regulatory signals that are recognized by various chromatin remodelers. The interaction between the remodeling ATPase and its target nucleosome is not only dependent on the intrinsic affinity between both components but can also be modulated by various accessory proteins as well as by post-translational modifications of all factors involved. DNA sequence features, additional RNA and protein factors as well as differential expression or alternative splicing of remodeler subunits increase the complexity of the remodeler–nucleosome interplay considerably. In addition, the underlying "remodeling code" that targets the action of many different complexes has to be highly dynamic in order to allow fast cellular responses to external stimuli. Since it is unlikely that every promoter is marked by a unique combination of features that can be recognized by a remodeler, it remains elusive how a robust identification of target genes is achieved. Thus, it will be interesting to further investigate how the cellular remodeling machinery balances the requirement for both precision and speed.

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