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Chromatin Remodelers and Their Way of Action

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1. Introduction

Chromatin is the packaged form of the eukaryotic genome in the cell nucleus, presenting the substrate for all DNA dependent processes. The basic packaging unit of chromatin is the nucleosome core, a nucleoprotein structure consisting of 8 histone proteins and 147 bp of DNA. Two of each H2A and H2B, H3 and H4, form an octameric, disc like particle on which 1.65 turns of DNA is wrapped [1]. Nucleosomal cores are separated by a linker DNA, with a varying length of 7 bp to 100 bp, with distinct lengths in different organisms and tissues. Even within one cell type the linker length can vary about 40 bp between the actively transcribed and repressed genes [2].

Binding of the DNA to the histone octamer and the bending of the molecule on the protein surface present a strong barrier to sequence specific recognition of the nucleosomal DNA molecule. That's why the packaging of DNA into nucleosomes and higher order structures is generally inhibitory to all kind of DNA dependent processes. To overcome DNA sequence accessibility problems, cells have developed mechanisms to open higher order structures of chromatin and to disrupt nucleosomes allowing the binding of sequence specific regulators. In general, two major mechanisms exist which regulate chromatin accessibility: First, histones can be posttranslationally modified and recruit specific effector proteins to chromatin [3]. Second, specific chromatin remodeling enzymes displace the histone octamers from DNA or translocate them on DNA, thereby exposing or protecting underlying DNA sequences to regulatory factors that control the DNA dependent processes [4].

The presence of 53 different chromatin remodeling enzymes in the human cell suggests specialized functions of these enzymes and the associated complexes. Chromatin remodelers are DNA translocases that apply an ATP-dependent torsional strain to DNA, providing the force to reposition nucleosomes; i.e. moving the histone octamer to a different site on the DNA [4,5]. Diverse remodeling enzymes and complexes have distinct nucleosome positioning

activities. In other words, the remodelers interpret the DNA sequence/structure information in different ways, establishing target site-specific nucleosome positioning patterns. The exact nucleosome positions at a given site depends on both, the type of the ATPase motor protein and the composition of the multiprotein complex where it is integrated [6]. The specialized functions of remodeling enzymes may result from their different nucleosome positioning behavior and the distinct targeting to genomic sites.

There is plenty of data available on the remodeling mechanism *in vitro*, however not much is known about the targeting and regulation of the remodelers *in vivo*. It remains unclear whether these complexes form a dynamic chromatin environment or a rather static chromatin structure with defined nucleosome positions in the cell nucleus. Many chromatin remodelers are believed to bind DNA and nucleosomes in a sequence independent manner *in vitro*, however there is mounting evidence for specific chromatin signals that are recognized by chromatin remodelers. This is best demonstrated by the recognition of histone variants, modified histone tails, the preferential binding to nucleosome free regions of DNA and binding to specific DNA and RNA structures and sequences. In addition, interacting proteins and/or accessory domains of the remodeling complexes may serve as an additional layer of signal recognition and recruitment of remodelers to the right place at the right time.

2. Remodeler families

The catalytic subunit of the remodeling enzymes consists of a conserved ATPase domain and unique flanking domains, used for a simplified separation into four distinct families (Fig. 1). The ATPase domain consists of two tandem RecA-like folds (DExx and HELICc), containing seven conserved helicase-related sequence motifs that classify the enzymes as part of the Superfamily 2 grouping of helicase-like proteins [7,8]. Chromatin remodelers are lacking the ability to separate nucleic acid strands, so they are not bona fide helicases. However, they are DNA translocases that use the energy of ATP to create a necessary force to reposition nucleosomes.

In a qualitative and quantitative study, the Snf2 family members were further subdivided into 24 distinct subfamilies based on similarities within the Snf2-specific motifs. Increased genomic complexity is paralleled by an increasing number of subfamilies and members of a given subfamily: the *S.cerevisiae* genome encoding some 6000 genes has 17 Snf2 family members belonging to 13 subfamilies, and the human genome encoding some 21000 genes has 53 Snf2 family genes from 20 subfamilies [8].

2.1. SWI/SNF family

The SWI/SNF complex was first described in *Saccharomyces cerevisiae*. In 1984 genetic screens revealed that the mutations in sucrose non-fermenting (SNF) genes caused defects in expression of the SUC2 gene, which is required for growth on sucrose and raffinose as a carbon sources [9]. Similarly, mutations in SWI genes were identified as defective for expression of the HO gene, which is required for mating type switching (the name Swi is derived from switching defective). Mutations in both SNF and SWI genes cause pleiotropic phenotypes,
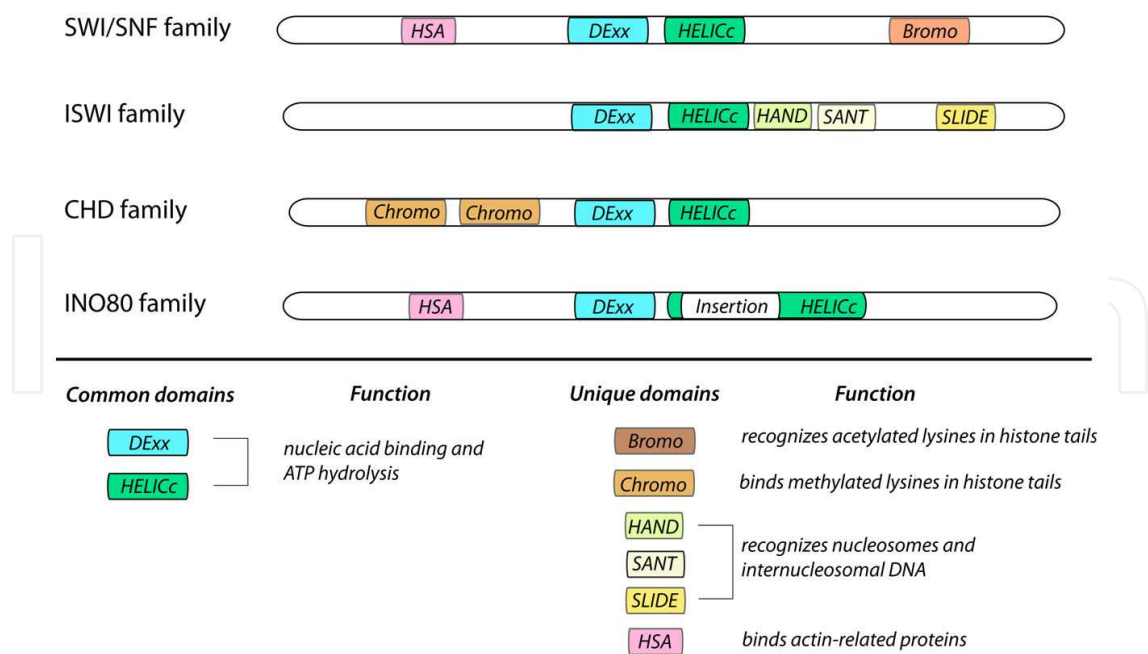
Figure 1. Classical organization of remodeler families defined by their catalytic domain. All remodeling enzymes consist of a shared ATPase domain and unique flanking domains.

suggesting a global role for Swi/Snf in gene expression. However, recent whole-genome expression studies have shown that Swi/Snf controls transcription of a small percentage of all *S. cerevisiae* genes [10]. The SWI/SNF family members are defined by the presence of an N-terminally located HSA (helicase-SANT) domain, which is known to recruit actin and actin-related proteins, and a C-terminally located bromo domain, suggested to bind to the acetylated-lysines of histones. This family of remodeling enzymes was shown to slide and to evict nucleosomes from DNA, but lacking chromatin assembly activities. Remodelers belonging to this family are large, multi-subunit complexes containing 8 or more proteins. Most eukaryotes utilize two related SWI/SNF family remodelers, built around the two related catalytic subunits Swi2/Snf2 or Sth1 in yeast, and BRM or BRG1 in humans (Table 1). Although SWI/SNF is not essential for yeast growth, a genome-wide analysis demonstrated that ~3 to 6% of yeast genes are regulated by SWI/SNF, with functions that contribute to both gene activation and repression [10,11]. On the other hand, RSC complex containing the Sth1 ATPase is essential for growth and about 10-fold more abundant than the SWI/SNF complex. RSC function is required for normal cell cycle progression [12]. Human BAF and PBAF complexes share eight identical subunits and are distinguished by the presence of only several unique subunits: BAF180, BAF200 and BRD7 for PBAF and BAF250a for BAF [13]. Variant subunits are thought to contribute to targeting, assembly and regulation of lineage-specific functions of those complexes. For example only PBAF, but not BAF, is capable of facilitating ligand-dependent transcriptional activation by nuclear receptors *in vitro* and to mediate expression of an interferon-responsive genes [14,15]. Both appear to be associated with lung cancer, as 90% of non-small cell lung carcinomas stained positively for BRG1 and BRM [16]. BRG1

possesses tumor suppressor functions, whereas BRM loss is a contributing factor and potential marker of tumorigenesis in lung, prostate and gastric cancers [17].

Complex	Catalytic subunit	Auxillary subunits	Organism
SWI/SNF	Swi2/Snf2	Swi1/Adr6, Swi3, Swp73, Snf5, Arp7, Arp9, Swp82, Snf11, Taf14, Snf6, Rtt102	Yeast
RSC	Sth1	Sth1, Rsc8/Swh3, Rsc6, Sfhl, Arp7, Arp9, Rsc1,2 or 4, Rsc7, Rsc30, Rsc3, Rsc5, Rtt102, Rsc14/Ldb7, Rsc10, Rsc9	
BAF	BRM or BRG1	BAF250, BAF155, BAF170,BAF60(A,B or C), SNF5, BAF57, BAF53(A or B), β-actin, BAF45(A,B,C or D)	Human
PBAF	BRG1	BAF180, BAF200, BRD7, BAF155, BAF45(A,B,C or D), BAF170,BAF60(A, B or C), SNF5, BAF57, BAF53(A or B), β-actin	

Table 1. Selected SWI/SNF family remodelers from yeast and human.

2.2. ISWI family

The ISWI (imitation switch) family ATPases harbour a C-terminal SANT domain adjacent to a SLIDE domain (SANT-like ISWI), which together form a nucleosome recognition module that binds to DNA and unmodified H4 tails [4]. The ISWI remodeling enzyme in *Drosophila*, is known to be present in several chromatin remodeling complexes such as NURF, CHRAC and ACF. Snf2H and Snf2L are the mammalian homologues of ISWI, which can act on their own or in the presence of one or more auxilary subunits forming different remodeling complexes with different properties. For example, Snf2H is known to interact with Tip5, RSF1 and WSTF proteins to form NoRC, RSF and WICH complexes. Specialized accessory proteins contain many chromatin binding domains, including histone fold motifs (in CHRAC), plant homeodomain (in Tip5), bromodomains (in BPTF, ACF1, Tip5) and additional DNA-binding motifs (HMGI(Y) in NURF301; AT hooks in Tip5). Many ISWI family complexes (ACF, CHRAC, NoRC) catalyze nucleosome spacing, promote chromatin assembly and confer transcriptional repression. However, NURF escapes theses general rules by disturbing nucleosome spacing and assisting ecdysone dependent transcriptional activation, showing that functional diversity is determined by the additional subunits [4]. The steroid hormone ecdysone directly modulates germline stem cells maintenance, activates transcription and proliferation in a cooperation with the NURF remodeler [18]. In *Drosophila*, loss of ISWI causes global transcriptional defects and results in dramatic alterations of the higher-order structure of chromatin, especially on the male X chromosome [19]. NoRC action correlates with specific changes in nucleosome positioning at the rDNA promoter region, causing heterochromatin formation and gene silencing [20].

Complex	Catalytic subunit	Auxillary subunits	Organism
NURF		NURF301, NURF55/p55, NURF38	
ACF	ISWI	ACF1	Fly
CHRAC		ACF1, CHRAC 14, CHRAC 16	
ISWI1a		loc3	
ISWI1b	ISWI1	loc2, loc4	
ISWI2	ISWI2	Itc1	Yeast
NURF	Snf2L	BPTF, RbAp46 or RbAP48	
ACF		ACF1	
CHRAC		ACF1, CHRAC17, CHRAC15	
NoRC	Snf2H	Tip5	Human
RSF		Rsf1	
WICH		Wstf	

Table 2. Selected SWI/SNF family remodelers.

2.3. CHD family

The CHD (Chromodomain-Helicase-DNA binding) family is defined by the presence of two chromodomains, arranged as a tandem, N-terminal of the ATPase domain. Additional structural motifs are used to further divide the CHD family into the subfamilies CHD1, Mi-2 and CHD7 [8,21].

Members of the CHD1 subfamily contain a C-terminal DNA-binding domain that preferentially binds to AT-rich DNA *in vitro* (members are Chd1 and Chd2 proteins in higher eukaryotes) [22,23]. Recently, the crystal structure of the DNA binding domain of Chd1, revealed a SANT-SLIDE like fold. This domain was shown to be required for the remodeling activity of Chd1 *in vitro* and *in vivo* [24].

The Mi-2 subfamily members contain a pair of PHD domains (plant homeodomain) in their N-terminal part (human Chd3 and Chd4, also known as Mi-2α and Mi-2β in *Drosophila*, respectively), implicated in nucleosome binding [25].

The CHD7 subfamily members have additional C-terminal domains, like the SANT or BRK domains (Chd5 to Chd9 proteins).

The biological properties of CHD family members are highly heterogenous. Some exist as monomers *in vivo*; others are subunits of multiprotein complexes, many of which have not yet been fully characterized [26]. The best studied is the NURD (nucleosome remodeling and deacetalase) complex, containing Chd3/Chd4, histone deacetylases (HDAC1/2) and methyl CpG-binding domain (MBD) proteins. It was shown to be involved in transcriptional repression of a specific set of genes during *C.elegans*, *D.melanogaster* and mammalian development [26]. Chd1 together with Isw1 are also termed nucleosome-spacing enzymes that are required

to maintain nucleosomal organization in yeast [27]. To date, Chd3, Chd4, Chd5 and Chd7 have been implicated in human disease processes. Chd3 and Chd4 have been identified as autoantigens in patients with dermatomyositis, a connective-tissue disease characterized by inflammation of both muscles and skin. Chd3 is associated with Hodgkin's lymphoma and Chd5 is associated with neuroblastoma, a malignant neoplasm of the peripheral sympathetic nervous system frequently affecting infants and children [28]. Haploinsufficiency of Chd7 in humans results in the CHARGE syndrome. Chd7 is essential for the develompment of multipotent migratory neural crest cells, which contribute to the formation of many tissues affected in CHARGE syndrome [29].

Complex	Catalytic subunit	Auxillary subunits	Organism
Chd1	Chd1		
Chd2	Chd2		*Fly*
NuRD	Mi-2	MBD2/3, MTA, RPD3, p55, p66/68	
Chd1	Chd1		
Chd2	Chd2		
NuRD	Chd3/Chd4	MBD3, MTA1/2/3, HDAC1/2, RbAp46/48, p66α/β, DOC-1?	*Human*
	Chd5	Unknown	
	Chd7	PARP1, PBAF complex	

Table 3. Selected CHD family remodelers.

2.4. INO80 family

The specific feature of the remodeling enzymes belonging to the INO80 (inositol requiring 80) family is the split ATPase domain. This unique module retains ATPase activity, and acts as a scaffold for the association with the RuvB-like proteins, Rvb1 and Rvb2. RuvB is a bacterial ATP-dependent helicase that forms a double hexamer around Holliday junctions to promote their migration during homologous recombination [30]. Unlike remodelers of other families, the INO80 complex exhibits DNA helicase activity and binds to specialized DNA structures *in vitro.* These DNA structures resemble Holliday junctions and replication forks consistent with the function of the complex in homologous recombination and DNA replication [31,32]. Yeast INO80 was shown to control the genome-wide distribution and dynamics of the histone variant H2A.Z. INO80 and SWR1 were shown to exhibit histone-exchange activity, being capable to replace nucleosomal H2A.Z/H2B with free H2A/H2B dimers [33,34]. Both remodeling complexes can slide nucleosomes *in vitro* on a reconstituted chromatin template and evict histones from DNA [35-37]. In addition to the role of INO80 in recombination and DNA replication, it is suggested to regulate the transcription level of about 20% of the yeast genes and to participate in DNA double-strand break repair via the interaction with γ–H2AX and recruit the MRX and Mec1 complexes to the DNA damage site [33].

Complex	Catalytic subunit	Auxillary subunits	Organism
INO80	Ino80	Rvb1, Rvb2, Arp5, Arp8, Arp4, Act1, Taf14, Ies1, Ies2, Ies3, Ies4, Ies5, Ies6, Nhp10	Yeast
SWR1	Swr1	Rvb1, Rvb2, Arp6, Arp4, Act1, Yaf9, Swc4/Eaf2, Swc2, Swc3, Swc4, Swc5, Swc6, Yaf9, Bdf1, Swc7, H2AZ, H2B	

Table 4. Selected INO80 family remodelers.

3. Translocation mechanism of chromatin remodelers

Chromatin remodelers use the energy of ATP hydrolysis to assemble, reposition or evict histones from DNA. Nucleosome repositioning by remodelers can be described as a 3-step mechanism: 1) initiation step that requires the recognition and specific binding to the substrate, 2) several translocation steps with varying step-lengths and kinetics depending on the particular remodeling enzyme and on the properties of the underlying DNA sequence, 3) release step, which occurs at energetically favourable positions depending on the combination of remodeler and DNA sequence/structure at this site [6,38]. This chapter will focus on the mechanisms of the translocation step.

Proposed models for nucleosome remodeling suggest that only a minor fraction of the 358 direct and indirect histone-DNA interactions are disrupted at a given time of the reaction, as the energy of ATP hydrolysis would not be sufficient to fully disrupt the nucleoprotein structure [39,40]. One of the first mechanisms proposed, is the ''twist diffusion model'' describing moving of the DNA over the histone octamer surface in 1 bp intervals. Thus, a single base pair distortion is continuously propagated through the nucleosome, transiently storing one additional basepair in the realm of the nucleoprotein structure. This model is supported by nucleosomal crystal structures exhibiting such a single-basepair "twist defect" [39,41]. However, several studies could not confirm such a translocation model. Experiments using nicked or gapped DNA substrates that uncouple DNA rotation mediated processes still allowed SWI/SNF and ISWI dependent nucleosome remodeling, arguing against a sole twist-diffusion mechanism [42-44].

Alternatively, it was suggested that nucleosomes are repositioned according to the ''loop recapture model'', proposing a detachment of a DNA segment from the histone octamer surface at the entry site of the nucleosome. The exposed octamer surface would interact with more distant regions of the DNA molecule, resulting in the formation of a DNA loop on the histone octamer surface. This DNA loop would translocate over the octamer surface in an energy-neutral process, by releasing and rebinding adjacent sequences on the protein surface. DNA loop propagation would change the translational position of the nucleosome, according to the size of the DNA loop [45]. This model is strengthened by biochemical and recent single molecule studies. ACF remodeling complex was shown to cause the unwrapping of DNA,

roughly 20 and 40 bp, from the nucleosomal border [46]. ATP dependent translocation of SWI/SNF and RSC on DNA and nucleosomal templates produces DNA loops and nucleosome remodeling by RSC was shown to produce a remodeled intermediate containing internal DNA loops [47].

Nucleosomal translocation and its step-size depend on the size of the DNA loop, a parameter that depends on the nature of the remodeling enzyme. Single molecule studies with the remodeling complex ACF suggested an initial step size of 7 bp and subsequent steps of 3-4 bp [48], whereas RSC was shown to exhibit a step size of 2 bp [49]. Within a strong nucleosomal positioning sequence both recombinant *Drosophila* Mi-2 and native RSC from yeast repositioned the nucleosome at 10 bp intervals, which are intrinsic to the positioning sequence. Furthermore, RSC-catalysed nucleosome translocation was noticeably more efficient when beyond the influence of this sequence. Interestingly, under limiting ATP conditions RSC preferred to position the nucleosome with 20 bp intervals within the positioning sequence, suggesting that native RSC preferentially translocates nucleosomes with 15 to 25 bp DNA steps [38]. Lately, it was proposed that loops do not freely diffuse about the exterior of the nucleosome but rather feed through specific restriction points by threading past fixed constrictions [47].

4. Targeting remodelers: Signals

One of the enigmas is the cellular requirement for 53 types of remodeling enzymes in humans that are capable to form hundreds to thousands of different remodeling complexes [6]. Such high numbers already suggest specialized functions for individual complexes and that remodeling enzymes mobilize nucleosomes in a specific manner. Many chromatin remodelers bind to DNA and nucleosomes in a sequence independent manner *in vitro*, albeit they exhibit complex specific features in nucleosome positioning and many of the complex subunits recognize specific chromatin features, targeting the complexes to defined genomic regions *in vivo*. The redundancy of enzymes and remodeling complexes suggest that they establish local and context specific chromatin structures and thereby regulate the DNA dependent processes. This chapter addresses the known and potential targeting mechanisms via DNA binding factors, the recognition of local chromatin features via functional RNA molecules and the impact of sequence context on the local chromatin structures (Fig. 2).

4.1. Direct chromatin targets

4.1.1. DNA and RNA sequence/structure

Mechanistical analysis of the nucleosome remodeling process revealed that binding of a remodeling complex to a mononucleosomal substrate results in a specific and ATP-dependent repositioning of the nucleosome on the DNA [50,51]. An *in vitro* study compared 7 different remodelers on different nucleosomal templates [6]. It appeared that each enzyme placed the nucleosomes at distinct positions and that even the same remodeling enzyme present in a
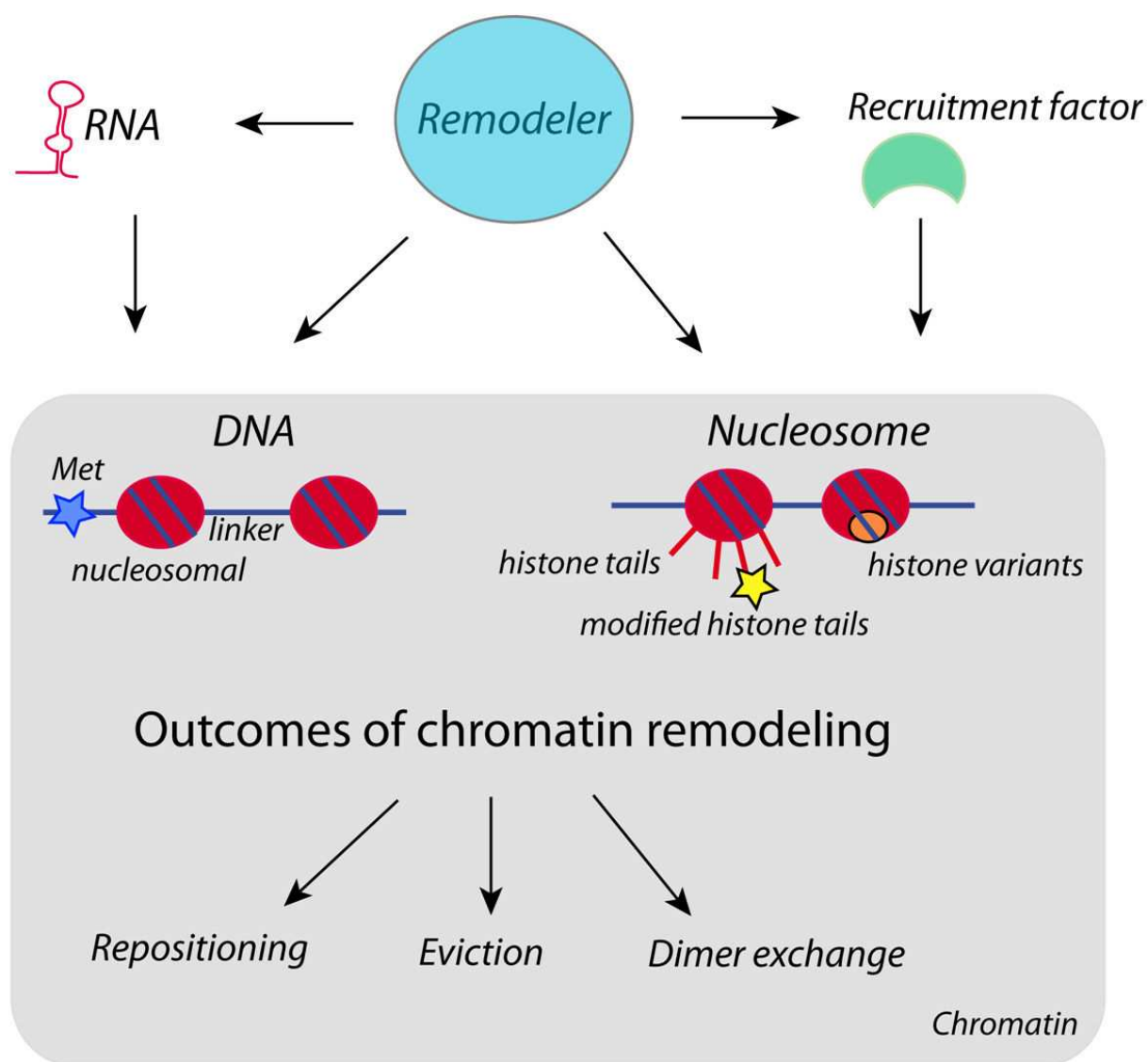
Figure 2. Targeting signals for chromatin remodeling complexes.

different complexes with various non-catalytic subunits, changed the outcome of the remodeling reaction (Fig. 3). Additionally, recent genome-wide studies compared 4 different remodeling complexes and similarly, it was observed that each remodeler exhibits a unique set of genomic targets correlating with distinct chromatin signatures [52]. Thus, these data suggest that the remodelers are capable to recognize the underlying DNA sequence/structure and accordingly establish specific chromatin structures.

The remodeling complexes contain DNA-binding motifs that are present in the catalytic or/and in accessory subunits (Fig. 1). For example, catalytic subunit Snf2H contains a SANT-SLIDE domain and in addition the WAC and AT hook motifs in the Acf1 and Tip5 proteins [4, 53-57]. These modules allow the specific recognition of DNA sequences and determine the outcome of a remodeling reaction, as it was shown by exchanging such domains between remodeling enzymes [38,58-60]. Nucleosome positioning is most probably affected by the
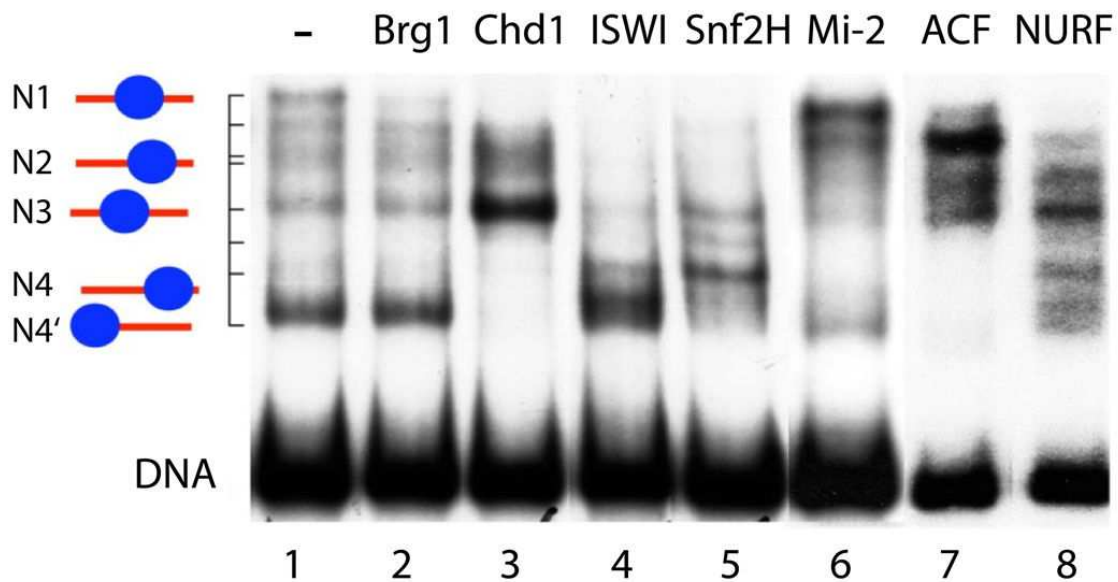
Figure 3. Bandshift assay showing that the chromatin remodelers position nucleosomes in a DNA sequence-specific manner. The 350 bp DNA, containing the hsp70 promoter sequence, was assembled into the nucleomes via salt dialysis. Five different single-nucleosomes were observed in the bandshift assay (mapped as N1, N2, N3, N4 and N4') and this was used as a substrate for seven recombinant chromatin remodelers (lane 1). Brg1, Chd1, ISWI, Snf2H, Mi-2, ACF and NURF in the presence of ATP repositioned nucleosomes in a remodeler-specific manner (lanes 2-8) [6].

different binding affinities of those motifs to the non-remodeled and remodeled substrates and the sequence dependent flexibility and stability of the particle, impacting the final outcome of the reaction. The role of specific DNA sequences in nucleosome positioning was shown for the ISWI-containing complex ACF, which positions a nucleosome relative to an intrinsically curved DNA sequence element [6].

Not only individual positions, but also internucleosomal distances depend on the DNA binding domains of the enzymes. ACF interacts with linker DNA and is capable to sense its length [61]. This structural element appears to play a key role in the positioning of nucleosomes in regular arrays, as the remodeler-induced mobility of the nucleosome is biased towards the longer flanking DNA [62]. Similarly, the Chd1 remodeler was described to sense the length of linker DNA [63].

Moreover, unusual DNA structures like quadruplexes could represent specific targeting signals. ATRX recognises G-rich repeat sequences, which are prevalent in telomeres [64]. These repeat sequences likely to form G-quadruplex (G4) structures, and ATRX preferentially binds to such a G4 structure *in vitro*. Such alternative DNA structures are believed to destabilize the genome and it is enticing to think that ATRX is responsible for stabilizing G-rich regions of the genome by remodeling G4 DNA and incorporating H3.3-containing nucleosomes [64].

Methylated CpG islands in the DNA were shown to be recognized by MBD (methyl-binding domain) domains, so it can serve as a targeting signal for particular remodelers. For example, MBD2 recruits the NuRD complex to methylated promoters [65]. The related TAM domain (MBD-like) in Tip5, the noncatalytic subunit of the NoRC complex, does not recognise

methylated DNA, but binds to the pRNA (promoter RNA). The pRNA is folded into the hairpin-like structure which is bound by NoRC and participates in the recruitment NoRC to the rRNA gene promoter region [56,66-68].

4.1.2. Histone modifications

The histone code hypothesis suggests that individual covalent modifications of histones or combinations of these modifications are recognized by specific readers which determine downstream events [3]. Chromatin remodeling complexes contain histone code reader domains, allowing the targeting to specifically modified chromatin domains and thereby enabling the establishment of a remodeler dependent nucleosomal positioning landscape.

The SWI/SNF type of remodelers contain bromodomains, interacting specifically with acetylated lysines on the histone tails [69]. Acetylation of the histone H3 N-terminal tail facilitated the recruitment and nucleosome mobilization by SWI/SNF and RSC. Tetra-acetylated H3 tails, but not tetra-acetylated H4 tails, increased the affinity of RSC and SWI/SNF for nucleosomes, which is dependent on the SWI/SNF bromodomain, but is not further enhanced by additional bromodomains present in RSC [70]. By contrast, the SANT domain of the ISWI type of remodelers is known to interact with unmodified histone tails. The H4 tail has been shown to play a decisive role in ISWI remodeling, in that both, the complete removal of the H4 tail [71,72] and its site-specific acetylation suppress the remodeling action of ISWI [73]. Human Chd1 protein interacts with H3K4me2/3 via its double chromodomains, which fold into a functional unit. On the other hand, nucleosomal H3K4 methylation reduces the affinity of the NuRD complex for H3 tail binding. It was shown that the second PHD finger of Chd4 preferentially interacts with unmodified H3K4 and H3K9me3 [74,75]. Full-length NURF301 the large subunit of the ISWI containing NURF complex contains a C-terminal bromodomain and a juxtaposed PHD finger that bind H3K4me3 and H4K16Ac, respectively. However, a NURF301 isoform lacking these C-terminal domains is also detected in cells, suggesting that alternative splicing can change targeting signals and localisation of the complexes within the genome. It was concluded, that the specific recognition of the posttranslational marks by NURF is important for the regulation of primary spermatocyte differentiation in *Drosophila* [76].

4.1.3. Histone variants

Non-canonical histone variants differ from the canonical histones at the level of their primary sequence, which can range from a few amino acid changes to large domains. These variants show distinct regulatory mechanisms for their expression and deposition, resulting in the establishment of chromatin domains with specific properties. The exchange of canonical histones for the variant ones is an active process, requiring the activity of remodeling enzymes and the action of RNA and DNA polymerases that actively displace the histones from DNA [77].

Analyzing the dynamic changes in the composition of histone variants in nuclear-transferred embryos revealed that the donor cell-derived histone H3 variants H3.1, H3.2, and H3.3, as well as H2A and H2A.Z, were rapidly eliminated from the chromatin of nuclei transplanted into enucleated oocytes. In parallel to this removal, oocyte-stored histone H3 variants and H2A.X

were incorporated into the transplanted nuclei, while the incorporation of H2A and H2A.Z was minimal or not detected. The incorporation of these variant histones was independent of DNA replication suggesting an active process depending on the remodeling complexes [78].

An ATRX (α-thalassemia X-linked mental retardation protein) – Daxx (death domain associated protein) complex can effectively assemble H3.3-containing nucleosomes in murine embryonic stem cells. It was shown that ATRX recruits Daxx to telomeres, and both complex subunits are required for H3.3 deposition at telomeric chromatin [79]. Chd1 in *Drosophila* embryos is required for the incorporation of the H3.3 variant into the male pronucleus, enabling the paternal genome to participate in zygotic mitosis [80]. The exchange of H2A.Z for H2A by the yeast SWR1 complex is in mechanistical terms the best described model system. H2A.Z replacement studied *in vitro* occurs in a stepwise and unidirectional fashion, exchanging one H2A.Z-H2B dimer at a time. Thereby heterotypic nucleosomes, containing one H2A.Z and one H2A molecule are established as intermediates and the homotypic H2A.Z nucleosomes as end products are generated in a second exchange step. The ATPase activity of SWR1 is specifically stimulated by H2A-containing nucleosomes without active displacement of histone H2A. Remarkably, the addition of free H2A.Z-H2B dimers results in a further stimulation of its ATPase activity and the combined eviction of nucleosomal H2A-H2B and deposition of H2A.Z-H2B. These results suggest that the combination of H2A-containing nucleosome and the presence of free H2A.Z-H2B dimer act as effector and substrate for SWR1 to govern the specificity and outcome of the replacement reaction [81]. Chromatin remodeling enzymes are also involved in the modification and dynamics of the histone variant H2A.X, which is phosphorylated upon DNA damage and repair. The WICH (WSTF-Snf2H) chromatin remodeling complex exhibits a novel kinase domain capable to phosphorylate Y142 on H2A.X. Both proteins, WSTF and Snf2H were also shown to bind to H2A.X in co-immunoprecipitation experiments [82]. In addition, it was recently shown that the activity of the Lsh remodeling enzyme is necessary for the efficient phosphorylation of H2A.X at DNA double-strand breaks and the successful repair of DNA damage [83].

4.2. Indirect chromatin targets

4.2.1. Sequence specific DNA binding proteins

The DNA-sequence dependent recruitment of remodelers is not necessarily mediated by the remodeling complex subunits themselves but can also occur via transient interactions with other sequence specific DNA binding proteins. For example, the NuRD complex is recruited to the various promoters of the target genes via interaction with several transcription factors and co-regulators such as NAB2, Ikaros, FOG1, BCL11B and several other factors described by Brehm and colleagues [26]. Genome wide expression, genetic and biochemical analysis established that TramTrack69, MEP1, and the *Drosophila* remodeling enzyme Mi-2 cooperate to control transcription levels of target genes [84]. It was also shown that Mi-2 binds to SUMO and to SUMO-ylated proteins giving rise to the hypothesis that this is a common signal for the Mi-2 recruitment. Similarly, Brg1 containing complexes are targeted via Sox10 to two key target genes in the Schwann cells [85]. Recruitment of SWI/SNF to the target genes of ERα requires

the nuclear receptor co-activator protein Flightless-I, which then directly binds to both, the ER and the BAF53 subunit of the SWI/SNF complex [86]. The ISWI subfamily containing remodeling complex NoRC is directly recruited to the rRNA gene by the transcription factor TTF-I, inducing gene silencing and heterochromatin formation [56].

4.2.2. Poly(ADP-ribose) polymer

Several studies demonstrated the targeting of Chd4 to sites of DNA double strand breaks in a PARP dependent manner [87]. The enzyme was shown to bind to the poly(ADP-ribose) polymer *in vitro*. Also ALC1 binds to PAR via its macrodomain and is recruited to sites of DNA damage [88].

5. Targeting remodelers: Search mechanism

The human genome is packaged into some 30 millions of nuclesosomes that have to be organized into functional chromatin domains with specific local structures. In order to identify target sites or to detect nucleosomes that have to be repositioned, the remodeling complexes have to detect such sites in chromatin very quickly. Potential genome screening mechanisms by the remodelers are discussed in this chapter.

5.1. Release/termination model

In the seventies, JJ Hopfield introduced the kinetic proofreading mechanism for reducing errors in biological systems. He used Michaelis Menten kinetics to explain how enzymes discriminate between different substrates [89]. A similar kinetic proofreading mechanism can be used to describe the action of remodelers, where "good" substrates are characterized by a high affinity of the remodeler for the nucleosome substrate (low value of Michaelis-Menten constant K_M) and a high catalytic conversion rate k_{cat}, efficiently moving the nucleosome to the end position of the translocation reaction. Thus, the k_{cat}/K_M ratio is high as expected for an efficient catalytic process. The opposite would be true for "bad" nucleosomal substrates, i. e. having a low k_{cat}/K_M ratio. According to this model, remodeler bind to "good" substrates and move them as long, as they are converted to "bad" substrates, exhibiting a lower affinity for the remodeler. The remodelers are released from the low affinity substrates, a mechanism termed "release model" (Fig. 4). In an alternative ''arrest model'', all nucleosomal substrates are recognized with similar affinities, but remodeler has a slow translocation rate on a ''bad'' substrate. *In vitro* binding assays showed that the Chd1 and ACF complexes were bound with lower afiinity to the nucleosomes at positions that reflected the end points of the remodeling reaction, suggesting that those enzymes function according to the release model (Fig. 4) [6].

5.2. The continuous sampling mechanism

Many proteins in the nucleus, including several remodelers are highly mobile as revealed by fluorescence recovery after photobleaching (FRAP) experiments. For proteins that do not
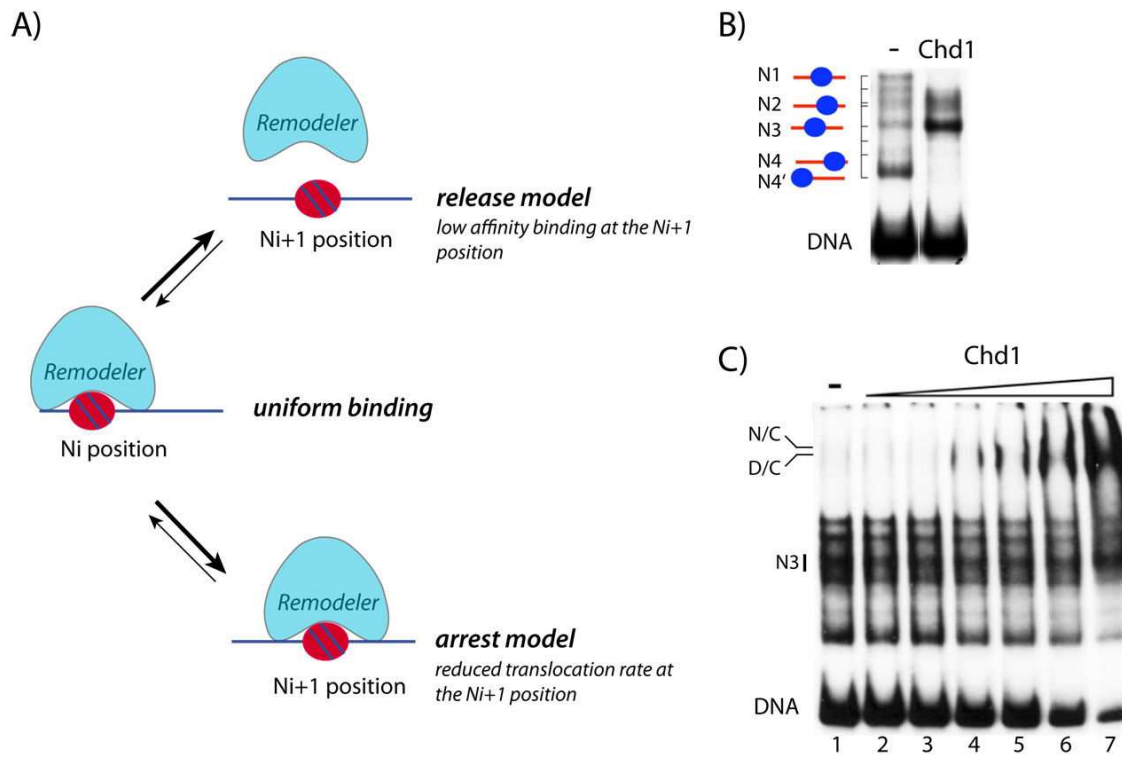
Figure 4. Model describing the affinity of remodelers to nucleosomes at different positions on the DNA. A) In the release model, the remodeling complex has a weaker binding affinity to the end-positioned nucleosome in comparison to any other nucleosome. In the arrest model, the remodeler binds all nucleosomes with similar affinity, but the translocation rate constant is much slower on a nucleosome present in the final position. B) Chd1 positions nucleosomes according to the release mechanism. Nucleosome position-dependent differences in the affinity of the remodeling complexes to the nucleosomal substrate were analyzed by bandshift assays. Remodeling reaction of Chd1 on mononucleosomal substrates reconstituted on a 350 bp DNA fragment containing hsp70 promoter region. Chd1 positions nulceosomes to the N3 and N2 positions. C) Binding reaction of Chd1 to the nucleosomes. The position of the DNA–Chd1 (D/C) and the nucleosome–Chd1 (N/C) complexes are indicated. The position of the N3 nucleosome is shown by a black box. Nucleosomes positioned at this site are bound by Chd1 with the lowest affinity. This position is at the same time the preferred endpoint of the remodeling reaction [6].

interact with any cellular structures, FRAP kinetics are a direct reflection of their translational motion properties. In contrast, proteins that bind to immobile structures such as chromatin, exhibit a slower overall mobility. The mobility of ISWI family remodelers Snf2H, Snf2L and Snf2L+13 (an ATPase inactive variant of the Snf2L) was studied in living U2OS cells. During G1/2 phase only 1-4% of the enzymes were immobilized [90], whereas the rest could be fitted by the free-diffusion model, suggesting only transient binding events. Additionally, chip-seq experiments with remodeling enzymes support the transient binding events. These experiments revealed that the localization pattern of wild-type Isw2p did not correlate with known sites of Isw2 function *in vivo*. In contrast, the catalytically inactive Isw2p–K215R was preferentially enriched at the known Isw2 target sites. This suggests, that in the absence of ATP hydrolysis the target sites remain high affinity binding sites, whereas the ATPase active enzyme does not bind to the remodeled nucleosomes [91]. These results indicate a continuous sampling mechanism (Fig. 5), by which the remodeler continuously screens the genomic nucleosomes for "good" substrates, converting them into the "bad" ones. Most of the binding

events seem to be unproductive, meaning that the remodeling reaction does not occur. From the experimentally determined relatively high remodeling enzyme concentrations (in the range of μM) 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, a combination of high remodeler concentrations, short residence times in the chromatin bound state and fast 3D diffusive translocations in the intervening periods appears to be an efficient mechanism to keep nucleosomes in place [90,92].
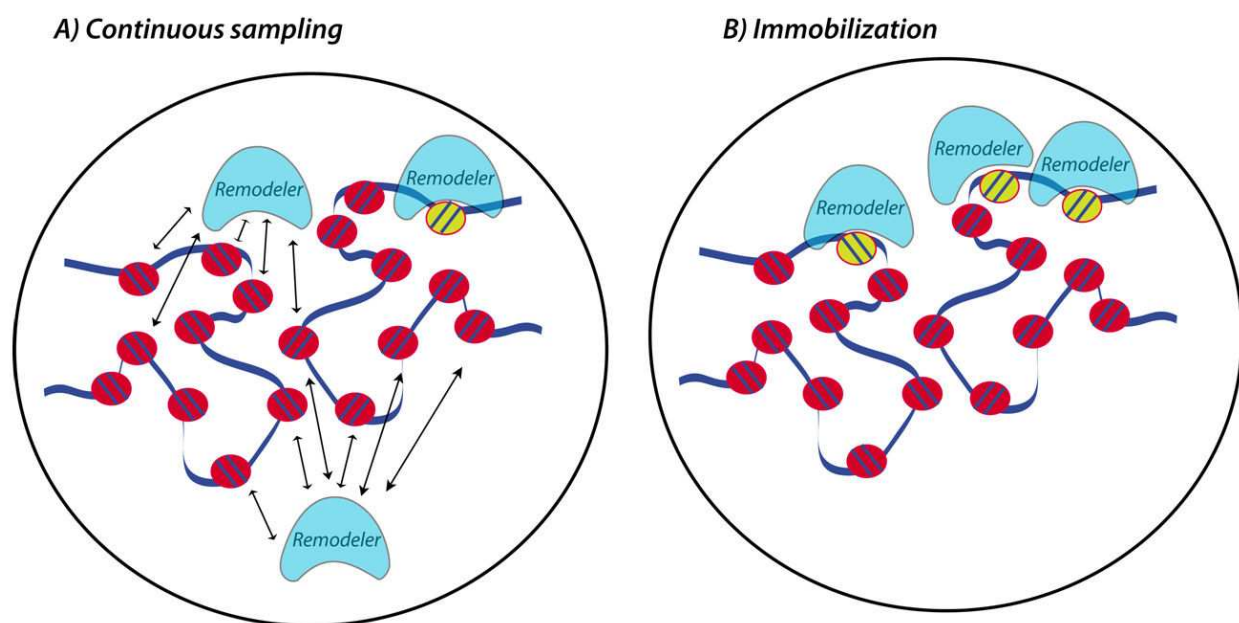

Figure 5. Genome-wide search for nucleosomal targets by remodeling enzymes. A) Continuous sampling mechanism. It is a diffusion-driven, rapid sampling of nonspecific sites with the remodeling enzymes binding only transiently to the nucleosomes. Most binding events are non-productive, as the nucleosomes are well positioned. B) Immobilization mechanism. Remodelers are recruited to the particular sites where they change nucleosomal positions. Targeting is achieved upon recognition of specific signals like histone modifications, chromatin-associated proteins, structural features of the chromatin environment or even by small molecules such as hormones.

5.3. Immobilization

In parallel with the continuous sampling mechanism, remodeling complexes are engaged by specific recruitment or immobilization at specific target sites. The respective mechanisms are described in chapter 4. For example, when cells were treated with dexamethasone, BRG1 and BRM were concentrated in a single spot in the nucleus, as revealed by immunofluorescence. The site coincided with the multimerized MMTV DNA and RNA FISH signals, showing that the enzymes are recruited to the MMTV array in a hormone-dependent manner. In this case the recruitment of the SWI/SNF machine results in the maintenance of an active chromatin structure that is compatible with transcription [93]. In other cases, like the nucleolar remodeling complex NoRC recruitment to the rRNA genes, continuous targeting results in gene repres-

sion via changes of the promoter nucleosome positioning that are incompatible with transcription initiation factor binding and further leads to the heterochromatin formation [20,94].

5.4. Nuclear dynamics of chromatin remodeling enzymes

Cells express a plethora of different remodeling complexes that act simultaneously on the cellular chromatin. The remodeler complexes diffuse freely through the nucleus, searching for "good" nucleosomes. "Good" nucleosomal substrates for the one machine may represent "bad" substrates for the other machine, suggesting that an active, free diffusing pool of remodeling complexes continuously changes the local chromatin structure. Upon specific signals individual machines are recruited to the specific sites to establish local chromatin structures correlating with a persistent activation or repression of certain DNA dependent processes. We hypothesize that the mixture of remodeling complexes in the cell, with their complex-specific remodeling patterns would continuously changes local chromatin structures, depending on complex that is currently recruited to such sites. Overall the action of the diverse remodeling complexes suggests that chromatin is continuously switching local nucleosome positions according to the levels, activity and set of remodeling complexes in a given cell [95].

6. Regulation of remodeler activity

As mentioned above, the individual accessory proteins of the remodeling complexes contain a diverse set of histones, DNA and nucleosome recognition motifs and these proteins change the outcome of nucleosome remodeling reactions. Accordingly, these proteins significantly determine the targeting to genomic regions and the qualitative outcome of a remodeling reaction. In this chapter, we want to focus on the regulation of the overall activity of remodeling enzymes by metabolites and modifications. Subunits of chromatin remodeling complexes often contain domains capable of recognizing specific posttranslational modifications on histone tails. However, significantly less is known about the functions of posttranslational modifications on remodeling complexes themselves and our understanding of its role is only beginning to emerge.

Phosphorylation. The first example of phosphoregulation of a remodeler was the mitotic phosphorylation of human SWI/SNF, which inhibits remodeling activity, with subsequent dephosphorylation by hPP2A restoring remodeling activity. It was suggested that the phosphorylated form would promote global repression of chromatin remodeling during mitosis [96]. In *Drosophila*, Mi-2 undergoes constitutive phosphorylation at N-terminus and CK2 was identified as a major kinase. Dephosphorylated Mi-2 displays increased affinity for the nucleosomal substrate, which in turn leads to an increased nucleosome-stimulated ATPase and remodeling activity. It was even postulated that it might be a common regulatory mechanism for CHD family remodelers [97]. Whether and how the phosphorylation alters the biochemical activity of INO80 is not known, but upon exposure to DNA damage, it was found that yeast INO80 complex is phosphorylated on the Ies4 subunit in a Mec1/Tel1-dependent manner [98].
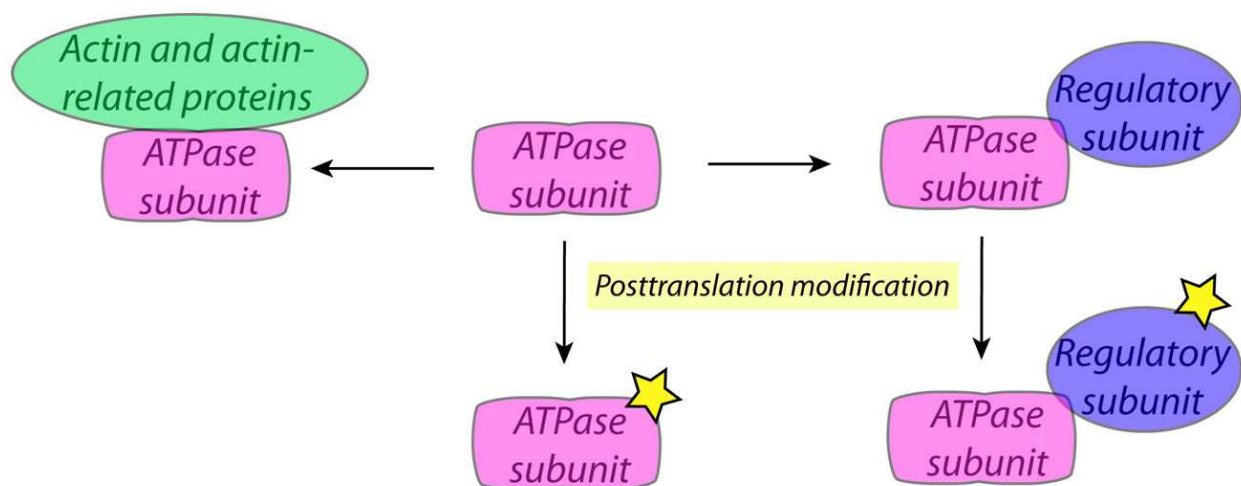
Figure 6. Different regulation possibilities of remodeler activity.

Acetylation. The acetyltransferase MOF acetylates TIP5, the largest subunit of NoRC, at position K633, adjacent to the TIP5 RNA-binding domain, and that the NAD(+)-dependent deacetylase SIRT1 removes the acetyl group. Acetylation regulates the interaction of NoRC with pRNA, which in turn affects heterochromatin formation, nucleosome positioning and rDNA silencing. Significantly, NoRC acetylation is responsive to the intracellular energy status and fluctuates during S-phase. Activation of SIRT1 on glucose deprivation leads to deacetylation of K633, enhanced pRNA binding and an increase in heterochromatic histone marks [99]. The acetylation of yeast Rsc4 does not significantly affect RSC catalytic activity or its ability to recognize acetylated nucleosomes, but K25 acetylation mark plays a key role in resistance to DNA damage, in a manner that appears to be regulated by its interaction with bromodomain 1. Moreover, Rsc4 acetylation acts in parallel with the INO80-remodeling complex to promote S-phase progression in cells subject to replication stress [100]. *Drosophila* ISWI is acetylated at position K753 *in vivo* and *in vitro* by the histone acetyltransferase GCN5. The acetylated form of ISWI represents a minor species presumably associated with the nucleosome remodeling factor NURF and may contribute during metaphase chromosome condensation [101]. Human Brm was shown to be acetylated at multiple locations, but two sites, clustered in the C-terminal region, appear to play a central role in the regulation. Mutation of these sites into non-acetylatable versions creates a Brm protein with increased activity in terms of inhibition of colony formation and transcriptional activation [102].

PARylation. In *Drosophila*, ISWI is poly-ADP-ribosylated (PARylated) by the enzyme PARP. PARylated ISWI binds weaker to the nucleosomes and DNA and displays weak nucleosome-stimulated ATPase activity. Moreover, the amount of ISWI bound to chromatin is affected by PARP activity, suggesting that PARP and ISWI might compete for common chromatin target sites and antagonize on chromosome condensation [103]. A different scenario is reported in the nucleolus of human embryonic kidney cell line, where PARP1/ARTD1-mediated parylation of TIP5, a noncatalytic subunit of NoRC complex, promotes the silencing of rDNA chromatin during replication. It is reported that upon of pRNA binding TIP5 undergoes

conformational change [67] which might favour the association of PARP1 and subsequently Tip5 is parylated. It was postulated that PARP1 enzymatic activity facilitates formation of silent rDNA chromatin and transcriptional silencing [104].

7. Conclusion

Global chromatin structure is a result of the combination of chromatin remodelers present in the cell. The ability to form various complexes with different activities and the concentration of the remodelers influences the nucleosomal positions genome-wide. Much data have been accumulated from *in vitro* experiments addressing the mechanistical questions of chromatin remodelers, but the recent studies have begun to reveal how these proteins find their place of action in the cell. From our current knowledge it seems that the local chromatin structures undergo a continuous change due to a continuous and random binding of different remodeling complexes. A large fraction of the remodeling complexes diffuse freely through the nucleus and act on nucleosomal substrates. In addition, the specific cellular signals are responsible for the fast recruitment of the individual machines to the specialized DNA sites correlating with a persistent activation or repression of particular DNA dependent processes, establishing persistent changes in chromatin structure.

Acknowledgements

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