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Sequence-specific targeting of chromatin remodelers organizes precisely-positioned nucleosomes throughout the genome

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Abstract

Eukaryotic genomes are functionally organized into chromatin, a compact packaging of nucleoproteins with the basic repeating unit known as the nucleosome. A major focus for the chromatin field has been understanding what rules govern nucleosome positioning throughout the genome, and here we review recent findings using a novel, sequence-targeted remodeling enzyme. Nucleosomes are often packed into evenly spaced arrays that are reproducibly positioned, but how such organization is established and maintained through dramatic events such as DNA replication is poorly understood. We hypothesize that a major fraction of positioned nucleosomes arises from sequence-specific targeting of chromatin remodelers to generate “founding” nucleosomes, providing reproducible, predictable and condition-specific nucleation sites against which neighboring nucleosomes are packed into evenly spaced arrays.

Keywords

chromatin modification; chromatin remodeling; genome structure; Isw2; nucleosome positioning; transcription

Introduction

Compaction of eukaryotic genomes into chromatin facilitates global packaging of genetic material and regulates accessibility of the underlying DNA sequence. Nucleosomes, the fundamental repeating units of chromatin, consist of a histone core wrapped by ~147 bp of duplex DNA. Wrapping of DNA into nucleosomes weakens potential interactions with many sequence-specific factors, both by occluding potential DNA binding sites facing inwards toward the histone core and by widening the major and minor grooves of DNA facing away from the core, distorting DNA structure from canonical B-form [1]. Nucleosomes are therefore broadly repressive in nature, and appear to play an important role in regulating DNA-dependent processes. For example, the location and density of nucleosomes can prevent transcription initiation outside of promoters [2, 3], regulate the timing and efficiency of replication origin firing [4–6], and control access of DNA repair machinery to sites of DNA damage [7]. The importance of understanding the mechanisms of nucleosome

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positioning arises not only from the tight integration of chromatin architecture with basic cellular processes, but also from the finding that many factors involved in nucleosome positioning are often mutated in cancers and other human diseases [8–10].

Using genome sequencing technologies coupled with micrococcal nuclease (MNase) or exonuclease (MNase-seq or ChIP-exo), the locations of nucleosomes have been extensively mapped in human, fly, worm and yeast cells [11–15]. Within each organism, nucleosomes show a striking conservation in positioning and distribution, particularly with respect to transcription start sites (Fig. 1). The regularity and reproducibility of nucleosome positions has raised the perplexing question of how cells establish and maintain defined nucleosome positions over multiple cell divisions. Previous work showed that while nucleosome are favored at some locations due to DNA sequence preferences [16], additional cellular factors are required for recapitulating the genome-wide patterns observed in vivo [17–19].

It is now well established that positioning nucleosomes into regularly spaced arrays relies on chromatin remodelers [17, 19]. Chromatin remodelers include several subfamilies of ATP-dependent enzymes that can alter chromatin structure using a helicase-like motor [20]. Each remodeler subfamily has a unique composition of domains and subunits that appear responsible for guiding the outcome of remodeling reactions, with distinct activities such as nucleosome assembly, nucleosome disassembly, histone exchange, and nucleosome repositioning [20]. How cells target particular remodeling activities to particular genomic loci, though, has been difficult to resolve. Many remodelers possess domains that recognize histone post-translational modifications (PTMs), such as bromodomains, chromodomains, and PHD fingers, that likely help localize remodeling activities [21]. However, PTMs are typically distributed over multiple neighboring nucleosomes, and it is difficult to envision how targeting via PTMs might be coupled to positioning nucleosomes over specific DNA sequences. Many remodelers also have DNA-binding domains, but these appear to be largely sequence-nonspecific in nature and therefore would not be sufficient for targeting [22–26].

Here we review our recent findings using a hybrid chromatin remodeler, where the native DNA-binding domain was replaced by a foreign, sequence-specific domain that targeted remodeling activity to defined loci throughout the yeast genome [27]. This work helped reveal a parallel endogenous mechanism for targeting a natural chromatin remodeler genome-wide via a transcription factor to produce precisely positioned nucleosomes. We also discovered that targeted nucleosomes were responsible for phasing local nucleosome arrays, and below we describe how sequence-targeting can help explain global nucleosome patterns.

Chimeric chromatin remodelers can specify nucleosome placement in *S. cerevisiae*

S. cerevisiae has proven to be an excellent model system for understanding the basis of nucleosome positioning, due to its relatively small genome size, ease of genetic manipulation, and extensive characterization of remodeling factors. We revisited nucleosome positioning at targets of the conserved Isw2 chromatin remodeler in *S. cerevisiae* to determine processes contributing to precise nucleosome placement across the genome. Early

in vivo studies showed that the Isw2 remodeler is coupled to transcriptional repression of early meiotic genes, and identified targeted Isw2 remodeling at *URS1* sites that required localization via the Ume6 transcription factor [28]. In contrast with Isw2, two remodelers with similar biochemical activities in vitro, Isw1 and Chd1, do not appear to have specific genomic targeting and instead are required for maintaining arrays of evenly spaced nucleosomes in coding regions [17]. Despite the relatively nonspecific functions in vitro and general lack of sequence preferences in vivo, Isw2 along with Isw1 and Chd1 are thought to be responsible for the organization of a large fraction of nucleosome positions in *S. cerevisiae*. In fact, for the *isw1*/*chd1*/*isw2* triple mutant, the well-defined, reproducible positions of nucleosomes across the yeast genome are completely abrogated [17].

A major area of interest in the chromatin remodeling field has focused on how the direction of nucleosome sliding is determined. Studying yeast Chd1 in vitro, we previously found that that the sliding direction could be dictated by attaching a foreign, sequence-specific DNA-binding domain [25]. By fusing a foreign binding domain in place of the natural, sequence-nonspecific DNA-binding domain, we showed that chimeric Chd1 remodelers preferentially shifted nucleosomes on top of target sites on DNA. Interestingly, a chimeric remodeler containing monomeric streptavidin also showed targeted remodeling, but displayed distinct outcomes depending on the locations of biotinylation sites [29]. When biotinylation sites were restricted to the DNA flanking the nucleosome, repositioning by the Chd1-streptavidin remodeler shifted biotinylation sites onto the nucleosomes, similar to the behavior of other Chd1 chimeras made with sequence-specific DNA-binding domains. For both types of remodelers, directional sliding appeared to arise from burial of the binding site on the nucleosome, which reduced accessibility and thus remodeler binding. For the Chd1-streptavidin remodeler, biotinylation of the histone tails yielded uncharacteristic behaviors for Chd1, resulting in mononucleosomes shifting past the ends of DNA and nucleosomes colliding into their neighbors [29]. These unique behaviors were consistent with remodeling activity being largely regulated through binding: targeting via histone tails allowed for continued remodeling, regardless of nucleosome positioning, whereas targeting via DNA led to directional sliding, where movement of nucleosomes on top of the binding site significantly weakened remodeler binding, promoting accumulation of positions with buried sites.

With their propensity for directional sliding, the chimeric Chd1 remodelers appeared well suited for challenging native nucleosome positioning systems in vivo, providing a unique tool for investigating how chromatin responds to site-specific perturbations. Given the known targeting of Isw2 remodeler via the Ume6 transcription factor, we generated a Chd1-Ume6 chimeric remodeler [27]. Consistent with in vitro results, in yeast cells the Chd1-Ume6 remodeler specifically repositioned nucleosomes adjacent to the *URS1* motif, resulting in burial of these Ume6 recruitment sites within nucleosomes (Fig. 2A). The precision and specificity of these nucleosome movements were remarkable, because locations of recruitment motifs could be readily identified by simply finding the positions where Chd1-Ume6 shifted nucleosome dyads.

Endogenous sequence-targeted chromatin remodeling is predictable and precise

There has been significant debate about the relative contributions of cis-elements like poly-A tracts and other sequence motifs and trans- acting factors like ATP-dependent chromatin remodeling proteins to global nucleosome positioning under biological conditions [16–19, 30, 31]. We investigated whether specific recruitment of endogenous chromatin remodeling proteins, which can similarly be targeted through DNA sequence motifs, may explain the reproducible nucleosome positions observed in *S. cerevisiae*. Although previous observations indicated cooperation between Isw2 and Ume6 [28], genome-wide analysis revealed that the natural targeting of Isw2 via Ume6 yields strikingly precise and predictable nucleosome positioning at hundreds of sites throughout the genome [27] (Fig. 2B). In contrast to the hybrid fusion Chd1-Ume6 remodeler, which moves nucleosomes onto the recruitment site until the motif is occluded, the endogenous Isw2/Ume6 system leaves a considerable gap of 30 base pairs between the Ume6 binding site and the edge of the closest, repositioned nucleosome. This maintained exposure of target binding sites strongly suggests an inhibitory mechanism that attenuates Isw2 action. The unexpected precision in movement of a single motif-proximal nucleosome suggests that the sequence-specific recruitment of Isw2 at Ume6 binding sites is highly reproducible, and encoded in the underlying DNA sequence.

While we only demonstrated this precise, genome-wide targeting for the interaction between Isw2 and Ume6, recent high resolution ChIP-exo experiments have uncovered a highly specific interaction of Isw2 at Reb1 sites [32], and similar Isw2 recruitment has been observed or suggested at many other transcription factor sites [33, 34]. In humans, a large number of transcription factors have highly organized proximal nucleosome patterns, and many of these require the Isw2-related SNF2H and SNF2L remodelers [35, 36]. More recently, endogenous nucleosome positions were recapitulated on salt-dialyzed chromatin using purified Isw2 in combination with the sequence-specific general regulatory factors (GRFs) Reb1 or Abf1, specifically at Reb1/Abf1 binding sites [37]. While previous work has implicated GRFs in establishing nucleosome positioning [32, 38–40], this groundbreaking study from the Pugh and Korber labs demonstrated in a highly purified system that up to 1/3 of genomic +1 nucleosome positions can be explained by remodeler positioning at motif-encoded GRF binding locations [37]. Together, these results suggest that targeting a chromatin remodeler through interactions with a sequence-specific transcription factor is likely a pervasive system for precisely positioning specific nucleosomes throughout eukaryotic genomes.

Sequence-targeted remodeling sets the phasing of organized nucleosome arrays

Although the precise nucleosome positioning achieved through transcription factor targeting would help explain reproducible nucleosome peaks observed genome wide, it was not clear whether hundreds of TF sites could specify thousands of unique nucleosome positions. Unexpectedly, the chimeric Chd1-Ume6 remodeler helped disentangle direct from indirect

effects. Both the chimeric Chd1-Ume6 remodeler and the natural Isw2/Ume6 system showed a limited range of influence, where nucleosomes were only shifted when within ~100 bp of the expected final locations. Despite this limited range, however, both remodelers catalyzed the repositioning of up to five nucleosomes neighboring the target site. This shifting of nucleosome arrays is consistent with the single targeted nucleosomes providing barriers against which neighboring nucleosomes are phased (Fig. 2). We expect that native, non-targeted remodelers such as Isw1 and Chd1 are likely responsible for these array shifts in *S. cerevisiae*, because these remodelers were previously shown to be required for array packing against transcriptional start sites in vivo and in purified systems [17, 37]. While barrier establishment and packing mechanisms have been proposed before [19, 41, 42], the underlying mechanisms were unresolved. The comparison of endogenous Isw2/Ume6 and synthetic Chd1-Ume6 remodeling at TF binding motifs clearly identify sequence-targeted nucleosomes as barriers themselves that can define the phasing for adjacent arrays. Through this array phasing from a remodeler-targeted barrier, precise positioning of nucleosomes covering roughly 1kb of genomic sequence can therefore be encoded in a single 6 base pair transcription factor binding motif.

Precise nucleosome positions may influence transcriptional effectors

Why might the cell require such a precise positioning mechanism? A straightforward explanation would be that reproducible nucleosome positions are required for faithful regulation of transcription. However, when Chd1-Ume6 was used to disrupt nucleosome positions in yeast, there was little discernible impact on mRNA transcription, although we found a modest role in regulation of cryptic ncRNAs [27]. Similarly, although deletion of Isw2 impacts the positions of nucleosomes in thousands of nucleosome depleted regions, there is minimal impact on steady-state mRNA transcription with modest induction of cryptic ncRNA [43–45]. These studies argue against a critical contribution of precise nucleosome positions to steady-state RNA levels. Perhaps exact nucleosome positions are more critical for directly regulating mRNA levels during large-scale changes in transcriptional program, such as those seen during diauxic shift [46] or quiescence [47]. An alternative explanation could be that nucleosome placement influences activity of other chromatin-regulated processes. Recently, in vitro studies have shown an activity dependence on inter-nucleosomal distances for chromatin modifying enzymes [48]. If histone modifying enzymes display a similar preference for specific nucleosome geometries in vivo, the precise positioning of nucleosomes imparted by a sequence-targeted chromatin remodeler might enhance or restrict local histone modification efficiencies (Fig. 3). Accordingly, there may be regulatory crosstalk between precisely positioned nucleosomes and histone modifying enzymes. Interestingly, in addition to localizing the Isw2 chromatin remodeling factor, Ume6 also recruits the histone deacetylase Rpd3 [49], although it remains to be tested whether Rpd3 activity is influenced by nucleosome positioning or spacing.

A “spring-loaded” mechanism, where chromatin remodelers initially position nucleosomes onto unfavorable sequences to allow for rapid relaxation to thermodynamically-preferred locations, has been observed during Kaposi’s sarcoma-associated herpesvirus reactivation in human cells [50]. In a case such as this, precise nucleosome positioning may help govern the activity of transcriptional activators. In one scenario, nucleosome placement may occlude

binding sites and thus directly compete with binding of transcriptional activators. It has been suggested that movement of nucleosomes on top of transcription factor sites leads to eviction of bound activators [51–55]. By controlling positions of nucleosome arrays, targeted chromatin remodelers likely regulate activator-mediated transcriptional programs. A second example of modulating activator function could occur when the proximity of a nucleosome to a DNA-associated activator can physically promote or restrict histone eviction. If sufficiently far from bound activators that recruit histone evicting remodelers like SWI/SNF [56–58] or Rsc [59], distal nucleosome positioning may prevent or limit histone removal, whereas closer placement could favor eviction. Regulation of histone eviction, likely commonly coupled to transcriptional activation, is therefore the product of a competition among one or more pairs of TF-remodelers and the thermodynamically preferred, "spring-loaded" nucleosome positions. We believe that the precision that is intrinsic to sequence-targeted chromatin remodeling is well-suited to crosstalk with transcriptional effectors, and future research efforts should help improve our understanding of the scope and impact of these interactions.

Sequence-directed nucleosome positioning supports fidelity and plasticity

Chromatin remodelers are known to shift nucleosomes from their thermodynamically preferred positions, providing a means for cells to switch between two defined chromatin states [50]. In addition to protecting nucleosome positions from thermodynamic fluctuations, the TF targeting we describe is well suited for quickly re-establishing nucleosome positions in the wake of disruptive processes like DNA replication. Such a mechanism offers a simple explanation for how precise nucleosome positions can be persist in a population of dividing cells (Fig. 4). Recent reports find that packing against GRFs including Abf1, Reb1, and Rap1 occurs immediately after passage of the replication fork [60], and that transcription factors are in direct competition with nucleosomes after replication [61]. Since transcription factors are thought to bind throughout mitosis [62] and nucleosomes can be organized immediately after replication [60, 63], TFs and GRFs can use transcriptional history, DNA-encoded sequence motifs, and sequence-targeted chromatin remodeling to quickly and faithfully reestablish proper nucleosome positioning after each cell division. The remarkably predictable nucleosome positioning at target loci in budding yeast reinforces the idea that precise, sequence-directed nucleosome sliding can be encoded in the genome, and an important question for future investigations is determining unique preferences for different remodelers and remodeler-TF combinations with regard to recruitment sites and nucleosome positioning.

An emergent property of global nucleosome positioning based on transcription factors is that it naturally allows for plasticity. While partnered TF/remodelers are well suited to faithfully re-establish nucleosome positions after dramatic events that erase the chromatin landscape such as replication, widespread transcriptional reprogramming that requires distinct, condition-specific nucleosome positions can be easily accomplished by toggling the availability of transcription factors that direct chromatin remodelers (Fig. 5). As previously described, the removal of specific remodelers can allow nucleosomes to shift to more thermodynamically preferred positions [50]. However, by varying the TF availability, either through transcriptional induction of condition-specific TFs, or transport different TFs

into/out of the nucleus, the pattern of nucleosomes could easily be altered in a locus-specific manner.

The dynamics of transcription factor binding is likely a critical parameter in sequence-targeted chromatin remodeling. For example, a distinct set of nucleosome positions has been demonstrated for budding yeast in a quiescent state [47], and we expect that changes in TF targeting of remodelers is likely responsible. When *S. cerevisiae* enters quiescence, the Xbp1 repressor is transcriptionally induced while Stb3 is translocated from the cytoplasm to the nucleus [64, 65]. If these sequence-specific transcription factors similarly interact with Isw2, they could reposition nucleosomes near Stb3 and/or Xbp1 binding sites genome-wide, thus imparting a genomic nucleosome repositioning response that is preprogrammed in the underlying DNA sequence. In agreement with this notion, nucleosome positions around Xbp1, Stb3, and other transcription factor binding motifs change reproducibly during yeast entry into quiescence, although the dependence on Isw2 has not yet been confirmed [47]. Similarly, for differentiated cells in multicellular organisms, the cell type-specific transcription factor repertoire may instruct unique yet programmed nucleosome positioning patterns through targeted chromatin remodeling. Notably, in humans, the IKAROS transcription factor anchors the NuRD chromatin remodeling complex at DNA targets [66], which may similarly lead to cell lineage-specific motif-proximal nucleosome positioning.

Other aspects of transcription factor dynamics can shape nucleosome positioning through associated chromatin remodeling. In response to specific stimuli, dynamic interactions of pioneer factors with ATP-dependent chromatin remodeling proteins can make “closed chromatin” regions more amenable to binding of secondary transcription factors [53, 67]. Conversely, steroid receptor binding can alter dynamics of pioneer factor associations [68, 69]. Pioneer factor activity therefore helps determine which chromatin regions are accessible for local nucleosome rearrangements thus fine-tuning the scope of targeted nucleosome positioning. On a larger scale, the immediate accessibility of nascently-replicated DNA adjacent to origins of replication may dictate the order of nucleosome domain establishment, where early-replicating DNA nucleates primary chromatin arrays, which may preclude or favor binding of transcription factors in later-replicating regions. The idea of self-organizing “ground states” for remodeler-driven nucleosome positioning was recently postulated for genome-utilizing processes like replication and transcription, and is an elegant potential mechanism for mediating genome-wide organization of chromatin through TF-remodeler interactions at specific DNA motifs [37]. A system that uses DNA-encoded motifs to bridge a sequence-specific binding factor to chromatin remodeling machinery is thus ideal for providing fidelity and precision in nucleosome positioning while simultaneously allowing for rapid and tunable response to changing conditions.

Conclusions and outlook

In *S. cerevisiae*, targeted remodeling occurs through TF-mediated remodeler recruitment at specific DNA motifs [27, 28, 37]. Targeting can also be achieved synthetically by creation of hybrid, sequence-specific chromatin remodeling proteins like Chd1-Ume6 [25, 27]. Is precise nucleosome positioning by TF-remodeler pairs fundamentally conserved in eukaryotes? An important future goal will be determining the extent of TF cooperation with

chromatin remodeling factors throughout eukaryotic genomes. The existence of precise nucleosome positioning at TF sites suggests a regulatory mechanism may exist for dictating the final position of remodeled nucleosomes, so it will be enlightening to uncover the mechanistic basis and evolutionary conservation of this precision. In some eukaryotic systems, histone modifications may significantly influence recruitment of chromatin remodeling proteins and/or transcription factors, so future work should consider interdependence of histone modifications, chromatin remodeling proteins, transcription factors, and nucleosome positioning. Additionally, since nucleosome positioning on genomic DNA arises from different remodeler classes working together [37], an important future undertaking will be deciphering the relative contributions of each remodeler type in vivo.

Sequence-targeting of chromatin remodelers both ensures high fidelity and enables plasticity of nucleosome positions required to support dynamic cellular processes. Given the striking changes in cellular programming and phenotype that can accompany widespread changes in chromatin organization, we expect that transcription factor recruitment of chromatin remodelers likely underlies global reprogramming observed in cell differentiation. Likewise, aberrant targeting or regulation of chromatin remodeling factors can explain some instances of global shifts in transcriptional programs correlated with cancer. An intriguing area for future research includes investigating the specific local effects on nucleosome placement by chromatin remodelers targeted through noncoding RNAs or three-dimensional folding [33, 70]. We expect that bridging chromatin remodeling to sequence-specific factors is a widespread mechanism for precise nucleosome placement contributing to the creation, maintenance, and dynamics of genomic nucleosome positions.

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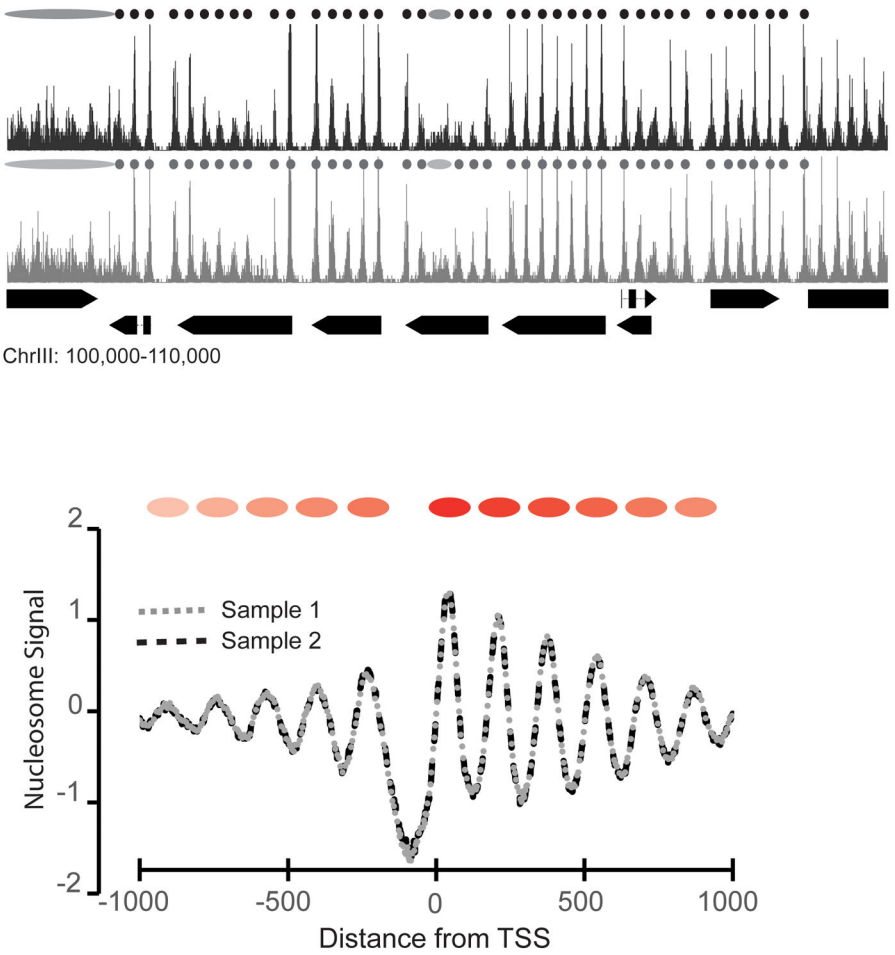

Figure 1.

Nucleosome positions are highly reproducible in *S. cerevisiae* cells. **Top:** Two representative genome browser images showing nucleosome dyads from MNase-seq experiments in independent *S. cerevisiae* isolates. Small circles denote well-positioned nucleosomes while large ovals represent poorly-positioned nucleosomes. Pointed rectangles denote annotated transcription units. **Bottom:** Overlay of nucleosome dyad signal at transcription start sites (TSS) for the two isolates in (from top). Red ovals represent positioned nucleosomes with respect to the TSS. Data was obtained from Gene Expression Omnibus (GEO) GSE72572 [27].

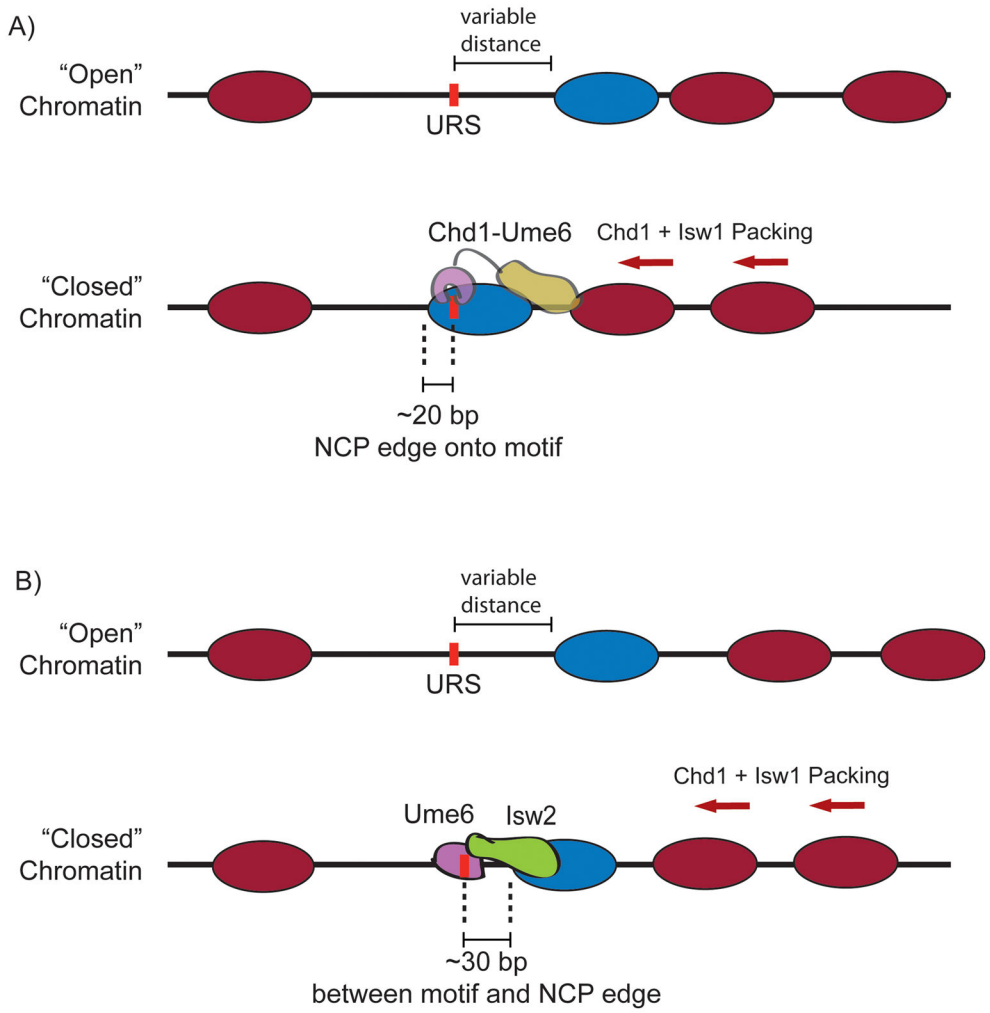

Figure 2.

Sequence-targeted chromatin remodeling in *S. cerevisiae*. **A:** Cartoon representation of sequence-targeted chromatin remodeling by a chimeric Chd1-Ume6 protein. Motif-proximal nucleosomes are mobilized toward the recruitment site until the recruitment motif is buried by ~20 base pairs of nucleosomal DNA. Distal nucleosomes are packed against this motif-proximal nucleosome to form a phased chromatin array. **B:** Cartoon representation of motif-proximal nucleosome positioning at Ume6 targets (*URS* sites) in *S. cerevisiae*. Through action of Ume6-recruited Isw2, motif proximal nucleosomes are moved toward the recruitment site to leave ~30 base pairs between the motif center and the nucleosome edge. Subsequent positioning of downstream nucleosomes is achieved through packing against the motif-proximal nucleosome barrier.

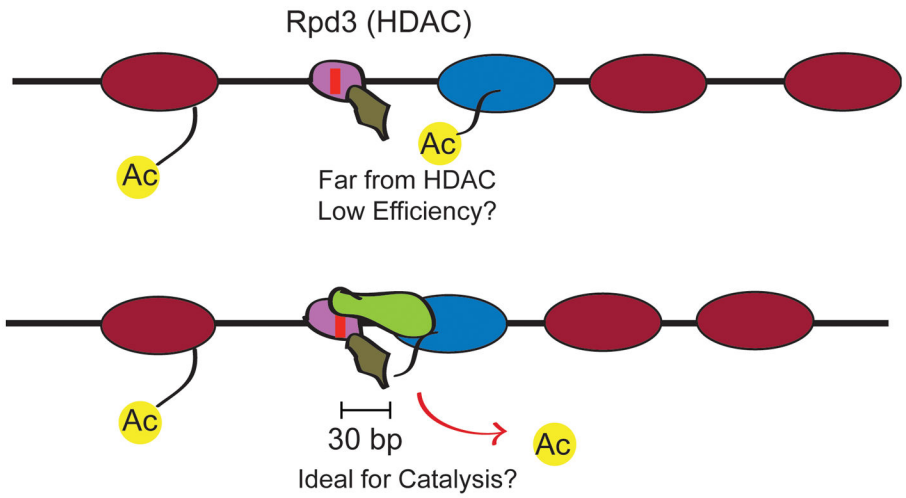

Figure 3.

Precisely-positioned motif-proximal nucleosomes may affect histone modification catalysis. Hypothetical situation where the action of a histone deacetylase (HDAC) such as Rpd3 is dependent on the distance of nucleosome substrate with respect to a recruitment site. (*top*) Low Rpd3 activity is achieved when nucleosome positions are not properly established. (*bottom*) Optimal histone deacetylation by Rpd3 occurs when the motif-proximal nucleosome is specifically positioned by sequence-targeted chromatin remodeling (eg the Isw2/Ume6 system).

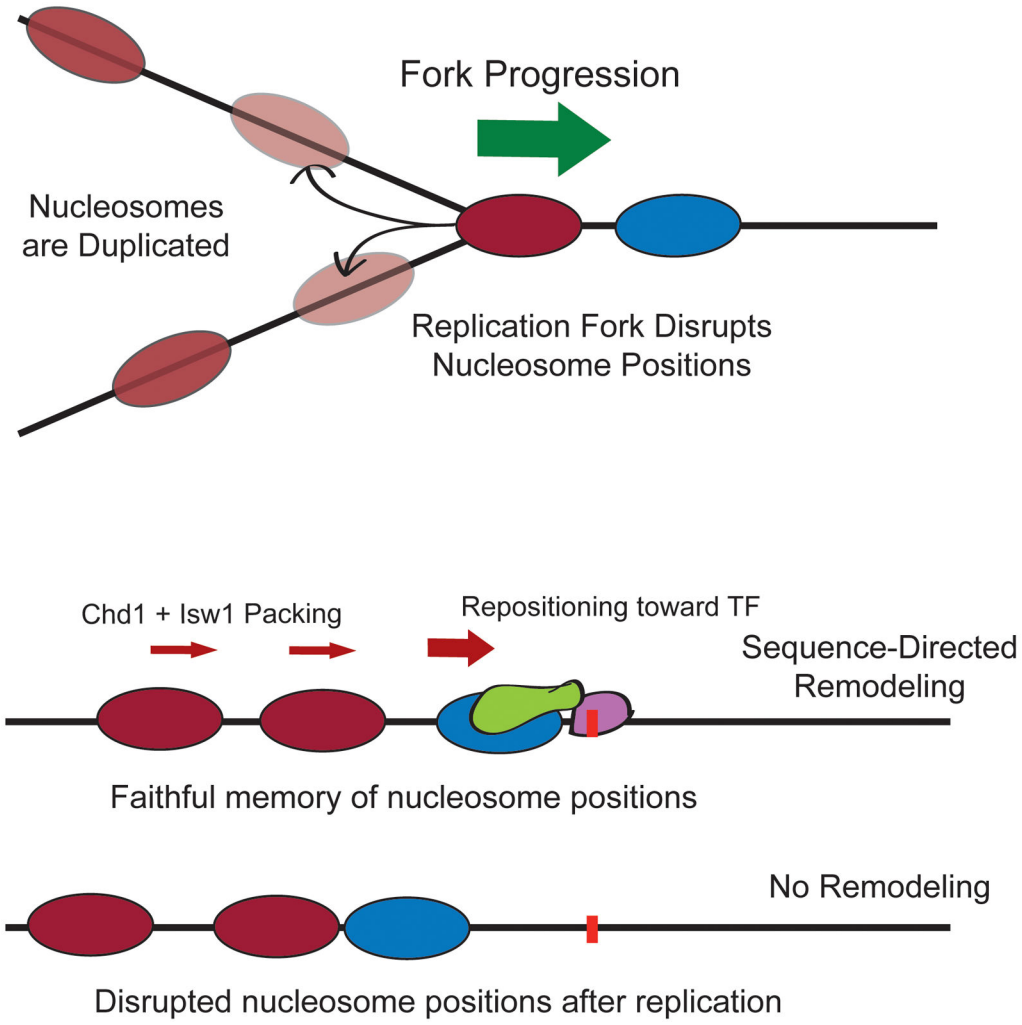

Figure 4.

Sequence-targeted chromatin remodeling can explain memory of nucleosome positions after replication. **Top:** As the replication fork moves through a DNA sequence, nucleosome positions are disrupted and need to be established on both DNA strands after replication. **Bottom:** Theoretical nucleosome positions after fork passage are shown in the presence or absence of targeted chromatin remodeling. Sequence-targeted recruitment of a chromatin remodeling factor can establish a precise motif-proximal nucleosome position on nascent DNA strands. Packing of distal nucleosomes against the motif-proximal boundary can reproduce the same nucleosome positions on newly-replicated DNA.

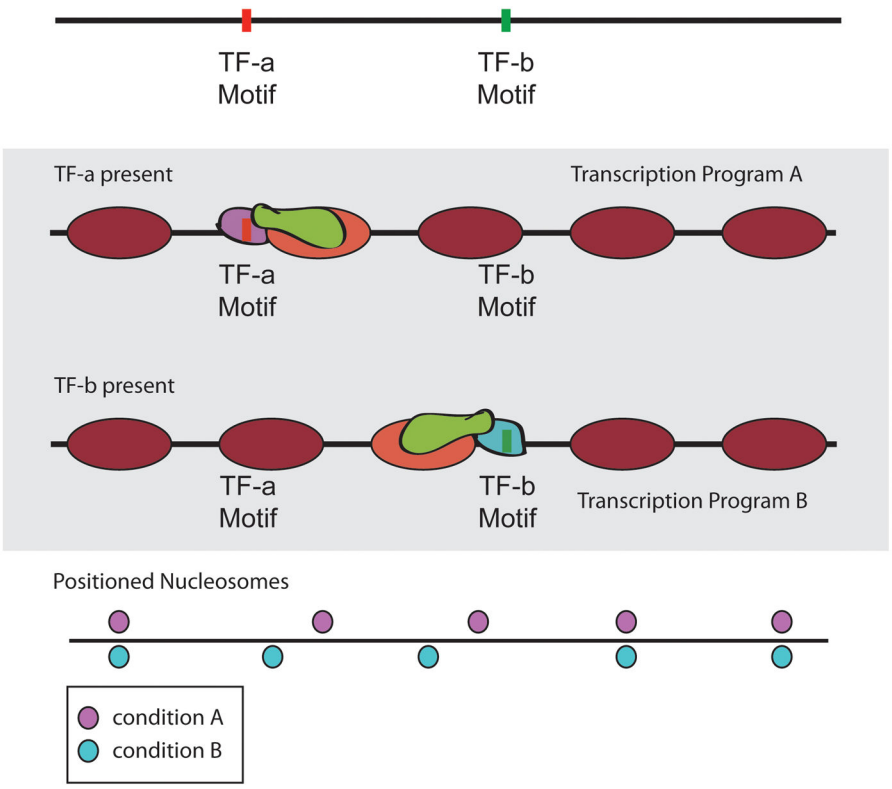

Figure 5.

Sequence-targeted chromatin remodeling allows for nucleosome positioning plasticity in different conditions. **Top:** Schematic of two hypothetical transcription factor (TF) binding sites on a DNA strand. **Middle:** Hypothetical nucleosome positions if a chromatin remodeling factor is targeted through TF-a or TF-b in a condition where the competing TF is not present. **Bottom:** Comparison of nucleosome positions under two distinct environmental conditions established through sequence-targeted chromatin remodeling.