J Biosci (2020)45:13
DOI: 10.1007/s12038-019-9970-7

Mini-Review

Picking a nucleosome lock: Sequence- and structure-specific recognition of the nucleosome

MATTHEW M MAKOWSKI[1,2], GUILLAUME GAULLIER[1,2] and KAROLIN LUGER[1,2]*

[1]*Department of Biochemistry, University of Colorado Boulder, Boulder, CO, USA*

[2]*Howard Hughes Medical Institute, Chevy Chase, MD, USA*

**Corresponding author (Email, karolin.luger@colorado.edu)*

The nucleosome presents a formidable barrier to DNA-templated transcription by the RNA polymerase II machinery. Overcoming this transcriptional barrier in a locus-specific manner requires sequence-specific recognition of nucleosomal DNA by 'pioneer' transcription factors (TFs). Cell fate decisions, in turn, depend on the coordinated action of pioneer TFs at cell lineage-specific gene regulatory elements. Although it is already appreciated that pioneer factors play a critical role in cell differentiation, our understanding of the structural and biochemical mechanisms by which they act is still rapidly expanding. Recent research has revealed novel insight into modes of nucleosome-TF binding and uncovered kinetic principles by which nucleosomal DNA compaction affects both TF binding and residence time. Here, we review progress and argue that these structural and kinetic studies suggest new models of gene regulation by pioneer TFs.

Keywords. Nucleosome; pioneer factors; transcription factors; transcriptional regulation

The same essential genome is replicated faithfully in nearly every one of hundreds of diverse cell types (and in ~37 trillion cells) in the human body. Differentiation into heterogeneous cell phenotypes from totipotent progenitors requires differential gene expression of the same underlying genetic information (Levine and Davidson 2005; Lee and Young 2013). During differentiation, genes might be turned 'on' during cell differentiation, as with lineage restricted genes, or 'off', for example pluripotency genes or genes specific to other lineages. Cell type classification often uses these global differences in gene expression patterns to categorize cell types based on the expression of characteristic lineage marking genes or gene sets (Regev *et al.* 2017). Many molecular mechanisms regulate differential gene expression. The nucleosome is a tertiary complex composed of 147 base pairs of DNA wrapped around an octameric complex of histone proteins. This DNA configuration effectively compacts and distorts the nucleosomal DNA, occludes much of the histone-facing DNA surface over its entire 147 bp, and presents a serious barrier to effective transcription (Luger *et al.* 1997; Kujirai *et al.* 2018; Farnung *et al.* 2018; Ehara *et al.* 2019; Zhou *et al.* 2019). Thus, one key mechanism of gene expression regulation is the compaction of transcriptional and gene regulatory elements by nucleosomes.

Gene regulation via nucleosome occlusion of a regulatory or transcriptional element, in the absence of other regulatory factors, depends only partially on the sequence of the element being occluded (Struhl and Segal 2013). Additional factors, notably the nucleosome positioning enzymes referred to as chromatin remodelers, actively position nucleosomes via complicated ATP-dependent mechanisms (Becker and Hörz 2002; Clapier *et al.* 2017). Chromatin remodelers themselves are only sometimes weakly specific for certain DNA sequence elements (Rippe *et al.* 2007).

This article is part of the Topical Collection: Chromatin Biology and Epigenetics.

Published online: 20 January 2020

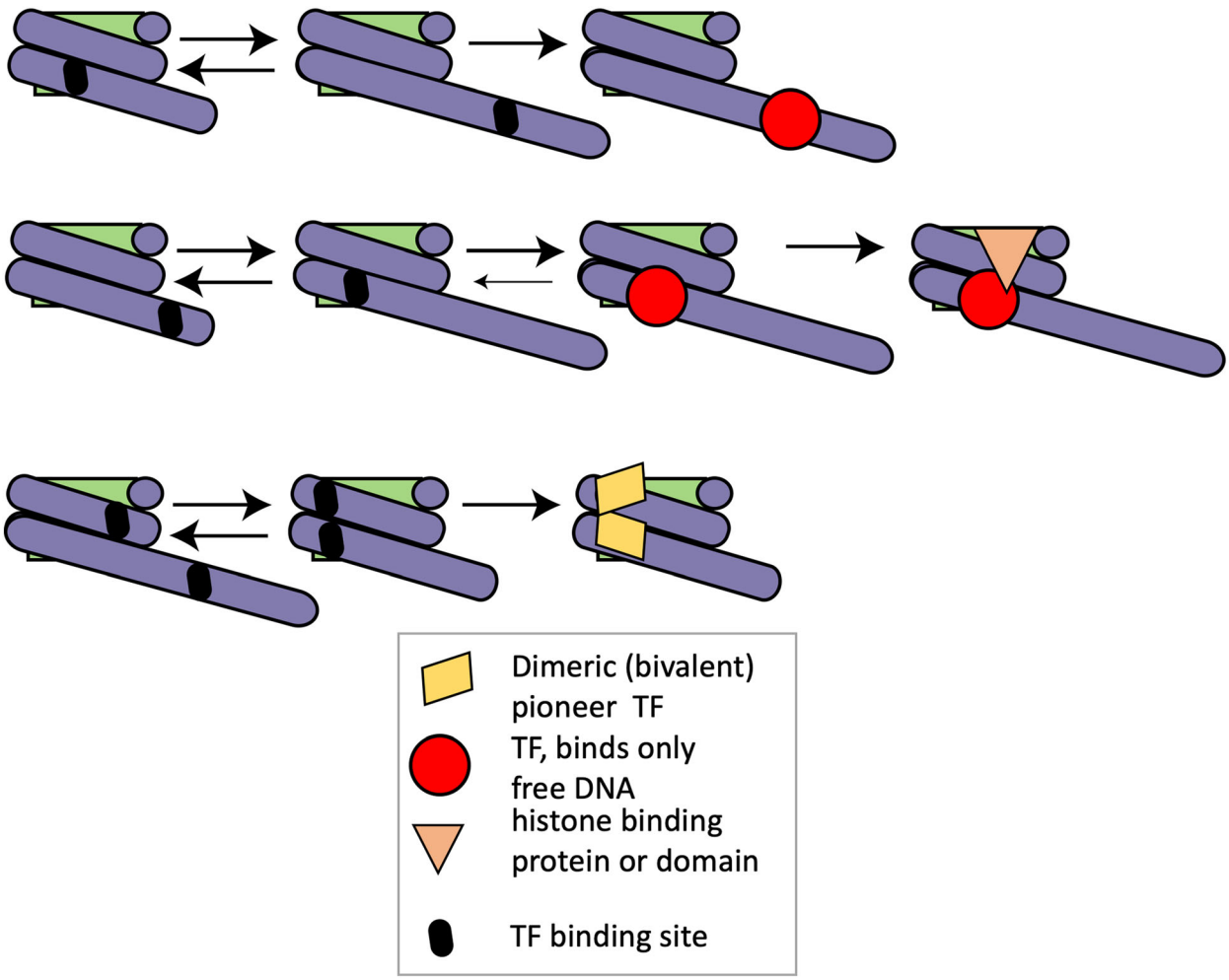

Figure 1. Nucleosome positioning by TF binding can occur through different mechanisms. Nucleosomes are repositioned either spontaneous or mediated by ATP-dependent chromatin remodelers; specific positions are stabilized by TF binding. Size of arrows denotes direction of equilibrium.

Instead, many sequence-specific transcription factors (TFs) recruit chromatin remodelers or the histone modification machinery and thus either directly or indirectly drive locus-specific chromatin remodeling *in vivo* (Lambert *et al.* 2018). Likewise, TF binding also has the potential to direct nucleosome position by restricting their mobility (figure 1).

TFs modulate nucleosome and chromatin structure using several different mechanisms (figure 2). First, TFs can directly recruit chromatin remodelers to place, position, or remove nucleosomes at a particular DNA element. Second, some TFs only recognize nucleosomal DNA when nucleosome 'breathing' occurs, that is when the DNA is partially and temporarily unwrapped from the nucleosome surface. This concept was pioneered by the late Jon Widom (Li and Widom 2004; Li *et al.* 2005), and it was later shown that histone post-translational modifications facilitate DNA breathing (reviewed in Bowman and Poirier 2015). TF binding facilitates further nucleosome unwrapping by promoting the binding of additional TFs, and/or in coordination with chromatin remodelers (Swinstead *et al.* 2016b; Fierz and Poirier 2019). Some TFs can bind their cognate motifs on fully compacted nucleosomal DNA and initiate ATP-independent DNA unwrapping or even histone eviction (Perlmann and Wrange 1988; Cirillo *et al.* 2002). However, outcomes in which TF binding stabilizes nucleosomes are also possible.

Most TFs are unable to bind preferred motifs if those motifs are embedded within nucleosomal DNA. In fact, early models proposed a competitive mechanism whereby TF binding precluded nucleosome formation in transcriptionally active regions (Workman 2006). On the other hand, TFs that have the ability to recognize their preferred motifs efficiently in the context of fully compacted nucleosomal DNA are referred to as

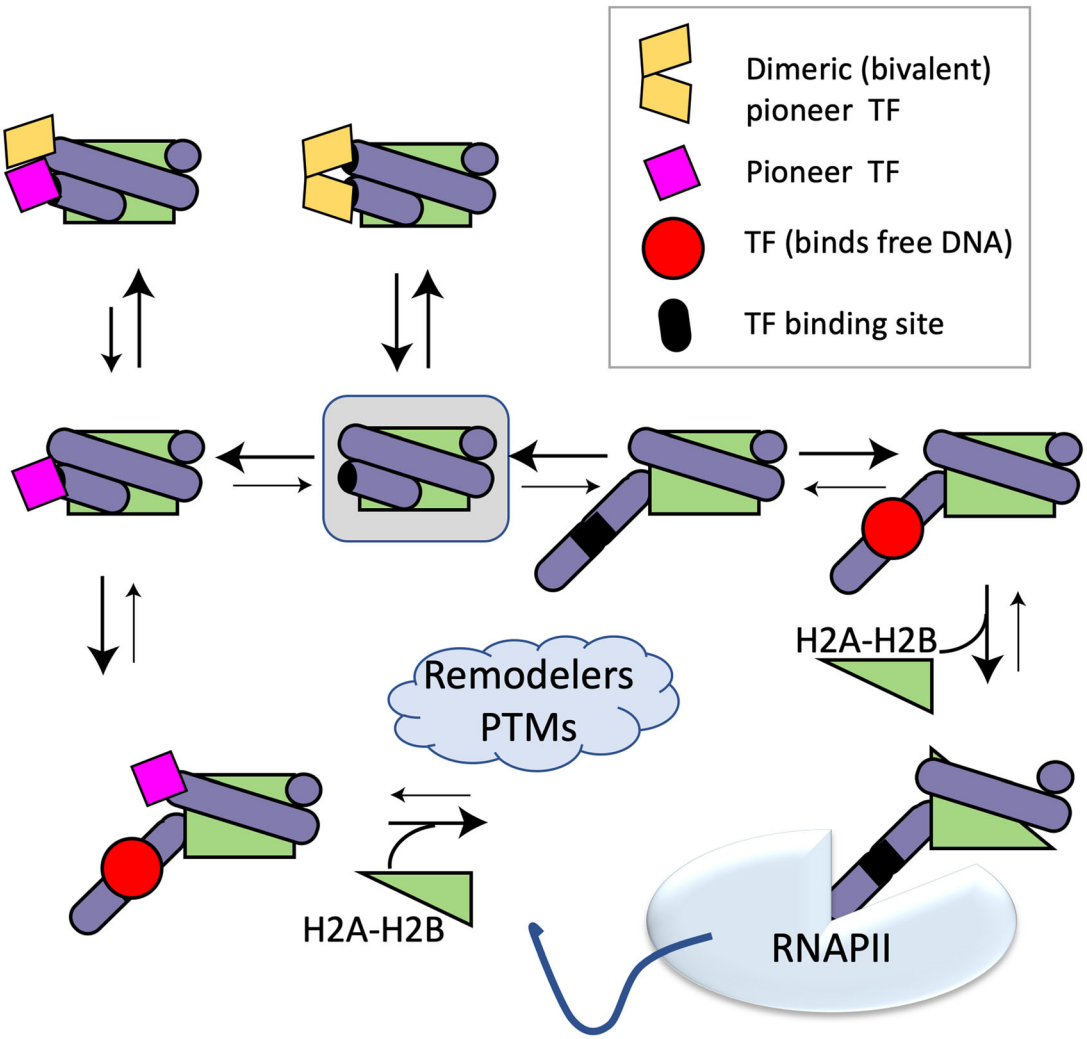

Figure 2. Modes of interactions between TF and nucleosomes. The majority of TF can only bind their cognate binding site when the DNA is partially released from the histone octamer. In contrast, pioneer transcription factors bind nucleosomal DNA. A special class of bivalent or dimeric pioneer TF could utilize the nucleosomal supergroove and/or additionally recognize the histone surface. Both types of TF can recruit ATP-dependent remodelers or histone modifiers to facilitate removal of H2A-H2B dimers, thereby promoting transcription by RNAPII. Length of arrow indicates direction of equilibrium.

'pioneer' TFs, as they bind at silenced regulatory sites to initiate lineage specific transcription (Zaret and Carroll 2011; Iwafuchi-Doi and Zaret 2014; Iwafuchi-Doi 2019). The consensus model of pioneer factor action is sequential. First, a pioneer factor binds its motif on a nucleosome and promotes partial unwrapping of the DNA. Then, additional TFs bind, unwrap the nucleosome fully (possibly in conjunction with chromatin remodelers and histone modifiers), and allow transcription (Reiter *et al.* 2017; Mayran *et al.* 2019). Different combinations of pioneer factors, expressed differentially early in differentiation, can thus drive cell fate decisions by transcriptionally activating lineage specific genes and gene regulatory elements.

However, pioneer factor activity and lineage specification must necessarily be more complex than this basic model. Genome-wide studies have shown that pioneer factors, like all TFs, typically show low or no occupancy at most of their preferred sequence motifs *in vivo* (Iwafuchi-Doi and Zaret 2014). Similarly, highly occupied sites differ from cell type to cell type depending on the cohort of other co-expressed TFs (Swinstead *et al.* 2016a; Zaret 2018). In other words, although pioneer factors can bind to nucleosomal sequence motifs, they exhibit site-selectivity even in genomic regions occluded by nucleosomes. Cooperative binding, relatively common among transcription factors (Mirny 2010; Jolma *et al.* 2015), is one means by which pioneer factors can select certain silent sites

for binding while rejecting other sites (figure 2, top row). The role of histone post-translational modifications in either directly or indirectly affecting TF binding (pioneer or not) is also under investigation (figure 3).

High-resolution structural details such as the rotational position of pioneer factor motifs around the nucleosome can substantially impact pioneer factor binding (Sekiya *et al.* 2009; Sahu *et al.* 2010; Cui and Zhurkin 2014; Soufi *et al.* 2015). Similarly, the location of the motif with respect to the histone octamer core affects pioneer TF binding. For example, FoxA1 is a canonical pioneer factor that prefers near-dyad binding (McPherson *et al.* 1993). In contrast, the widely studied TF and tumor suppressor p53 binds near the nucleosomal DNA entry and exit sites (Yu and Buck 2018). As yet another variation on this theme, the Yamanaka factor Sox2 does not exhibit a preference for a precise location of its site around the nucleosome, but rather whether the site faces inward or outward and whether or not the abundant nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP1) cooperatively binds with Sox2 (Liu and Kraus 2017). In addition to the motif itself, DNA shape features and motif density can also play a role in guiding

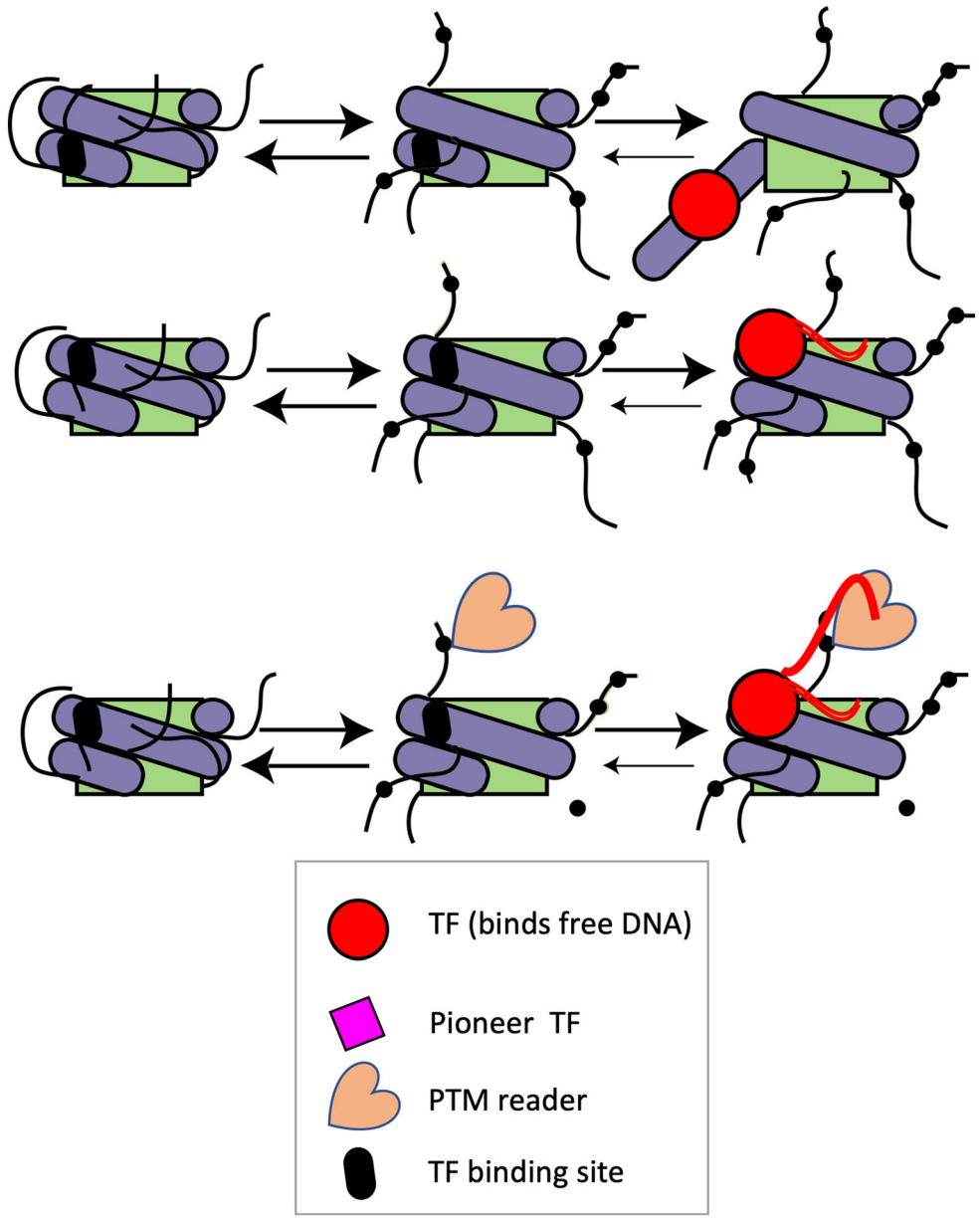

Figure 3. Histone post-translational modifications can regulate DNA accessibility. PTMs on histone tails (black lines) can promote TF binding either by increasing DNA breathing, increasing accessibility of nucleosomal DNA, or recruitment of PTM readers that in turn recruit TF.

nucleosome recognition by pioneer TFs (Ghosh *et al.* 2018). Furthermore, non-specific TF binding in the absence of a preferred motif can still induce strong pioneer factor–nucleosome interactions that are only a few fold weaker than in the presence of a strong motif (Sekiya *et al.* 2009; Yu and Buck 2018). With Satb1, a multimeric 'genome organizer' transcription factor that binds to nucleosomal DNA, a sequence-specific DNA binding domain confers sequence specificity but is not required for high-affinity nucleosome binding interactions (Ghosh *et al.* 2018). Some pioneer factors also possess direct histone interacting domains that regulate nucleosome recognition, for example the H3-H4 interacting C-terminal domain of FoxA1 (figure 1), although it is still unclear how common these domains are in sequence-specific TFs (Cirillo *et al.* 2002). There are currently no high-resolution cryo-EM or crystallographic structures of pioneer TFs bound to nucleosomes (reviewed in Zhou *et al.* 2019) despite one documented attempt (Takizawa *et al.* 2018), but structural studies fueled by the cryo-EM 'resolution revolution' will likely soon offer exciting insights into the atomistic details of TF-nucleosome interactions.

Apart from conventional biochemical and structural approaches, a recent *tour de force* study utilized a SELEX experimental design with high-throughput sequencing to identify nucleosome binding patterns for hundreds of transcription factors or DNA binding domains (Zhu *et al.* 2018). In addition to entry/exit site and dyad binding, this study uncovered a number of novel TF-nucleosome binding modes facilitated by the unique topography of the nucleosome. Of particular note was a cross-gyre or supergroove (Edayathumangalam *et al.* 2004) spanning binding mode. In this binding mode, two T-box family DNA binding domains (T and Tbx2) bound as a presumptive dimer to motifs separated by approximately 80 base pairs in sequence but spatially close to each other within the major supergroove of the nucleosome (figure 1). A number of T-box family DNA binding domains dimerize on DNA (Coll *et al.* 2002; El Omari *et al.* 2012; Newman *et al.* 2017) or in solution (Liu *et al.* 2016; Pradhan *et al.* 2016). Additionally, T-box supergroove binding reportedly stabilized the wrapped nucleosome (Zhu *et al.* 2018), as was reported much earlier for a bivalent small molecule (Edayathumangalam *et al.* 2004). Therefore, it seems reasonable to hypothesize that some T-box DNA binding domains can dimerize across the nucleosomal gyres and, by stably homodimerizing, prevent nucleosome dissociation (figure 2, top row). This hypothesis envisions a type of 'reverse' pioneer factor, a heretofore unreported means of repressing gene expression through stabilizing the nucleosome. How significant and common this mechanism of gene expression regulation is *in vivo* merits further study.

In addition to these recent developments in our understanding of the structural characteristics of TF and pioneer factor nucleosome binding, a recent kinetic study offered equally important insights into the molecular mechanisms by which pioneer factors act (Donovan *et al.* 2019). Slow off-rates and long residence times, as well as low mobility on chromatin (Sekiya *et al.* 2009), are proposed kinetic properties of pioneer factors, although there are some conflicting results in the case of FoxA1 (Sekiya *et al.* 2009; Swinstead *et al.* 2016a). These properties are justified under the assumption that pioneering action – unwinding or even evicting histones from a stable nucleosome – is expected to be a slow kinetic step. However, by definition, the binding affinity of a pioneer factor to a nucleosome should be the same, or nearly the same, as to free linear DNA (Zaret and Carroll 2011). Therefore, slower off-rates on chromatin and nucleosomes would necessarily be compensated by slower on-rates to maintain a similar equilibrium binding constant. And, for two yeast pioneer factors (Reb1 and Cbf1), a recent report demonstrates that this mechanism, referred to by the authors as dissociation rate compensation, is correct (Donovan *et al.* 2019). For Reb1, its slower dissociation rate on nucleosomes correlates with slow exchange in FRAP experiments *in vivo*. It remains unclear if this dissociation rate compensation mechanism is unique to a few select families or types of TFs, including Reb1 and Cbf1, or if it is instead common among most TFs with pioneer factor activity. In contrast, Rap1, another yeast pioneer TF, has shorter residence times on nucleosome arrays compared to linear DNA but still unwraps the chromatin fiber by inhibiting inter-nucleosome contacts and recruiting the RSC chromatin remodeler (Mivelaz *et al.* 2019).

What does this accumulated structural and kinetic information teach us about pioneer factor activity? In general, it seems increasingly clear that most TFs are repelled, often strongly, by nucleosomes, while the TFs that do bind nucleosomes tend to unwrap them (Zhu *et al.* 2018). One kinetic mechanism for nucleosome unwinding is dissociation rate compensation (Donovan *et al.* 2019); yet other kinetic mechanisms such as the one employed by Rap1 clearly exist (Mivelaz *et al.* 2019). In a broader sense, how do different structural modes of sequence-specific nucleosome recognition correlate with kinetic parameters of binding to and unwrapping of nucleosomal DNA? Does more severe dissociation rate compensation occur upon binding at some nucleosomal locations compared to others? How

do cooperative interactions among TFs (Adams and Workman 1995; Polach and Widom 1996) change the kinetic landscape? On the other hand, only a few TFs bind to and stabilize nucleosomes (Zhu *et al.* 2018), and it is uncertain how this nucleosome-stabilizing binding mode will relate to TF binding on free DNA. Do nucleosome-stabilizing TFs utilize a dissociation rate compensation mechanism? It is logical to suppose that nucleosome stabilization by a gyre-spanning dimer (or even a bivalent monomer) would co-occur with slower off-rates to maximize the duration of the stabilizing effect, yet this remains to be demonstrated.

In sum, the nucleosome represents an important means of regulating transcription in cells. But beyond acting as a simple transcriptional barrier, recent findings indicate that we should consider the nucleosome as a unique structural template that is recognized in a specific manner by transcriptional regulators. In the context of the nucleosome, DNA sequences can adopt new regulatory features that are not present in the strictly linear form, and the properties of nucleosomal DNA must be understood in terms of structure as well as in a time-dependent manner. Understanding the structural and mechanistic details of these nucleosome-specific TF functions will, in turn, inform a more sophisticated and nuanced picture of gene regulation and chromatin structure in the nucleus that incorporates activities that impinge on nucleosome structure and stability, such as ATP-dependent chromatin remodelers and the post-translational modification of histones.

Acknowledgements

This work was supported by the Howard Hughes Medical Institute and NIH R01CA218255.

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