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Mechanisms by which transcription factors gain access to target sequence elements in chromatin

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Transcription factors (TF) bind DNA sequence motifs, but the presence of a consensus DNA element is not sufficient to direct TF binding to chromatin. Recent genomic data have revealed that accessibility, as measured by DNase sensitivity and the presence of active histone marks, is necessary for TF binding. DNA sequence provides the initial specification of the accessibility of DNA elements within chromatin that permits TF binding. In yeast, it is known that poly(dA-dT) tracts directly encode low-nucleosome occupancy at promoters. Recent evidence suggests that CpG islands in mammals are inherently refractory to higher-order chromatin structure and remain accessible, despite favoring nucleosome formation *in vitro*. Taken together, these studies support a model for how accessibility originates and then propagates throughout regulatory cascades and development.

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Introduction

Specific DNA sequence elements are sufficient to direct transcription factor (TF) binding in prokaryotes; however, in higher organisms, chromatin often occludes TF binding [1–4]. In eukaryotes, DNA is wrapped around nucleosomes and forms higher order chromatin structures that restrict TF access. The first high resolution *in vivo* measure of the accessibility of chromatin structure came from the study of candidate heat shock genes [5]. DNase I footprinting revealed that the 5' end of *Hsp70* and *Hsp83* were highly sensitive to digestion before heat shock induction [5]. Post-translational modifications of histones provide an independent measure of chromatin structure. For instance, histone acetylation is associated with actively transcribed genes [6,7], but can also be a precursor to transcription and permit subsequent activation [8]. DNase I signals overlap with histone acetylation marks [9], suggesting that histone acetylation contributes to the molecular basis for DNase I sensitivity. Multiple types of histone acetylation and H3K4 methylation often co-occur and are associated with transcriptionally active or potentiated chromatin [10••,11,12••,13]. Recently, André Martins developed a probabilistic model that infers DNase I sensitivity from histone modification data, reinforcing the qualitative link between DNase sensitivity and active histone marks with a quantitative model [14•] (Figure 1).

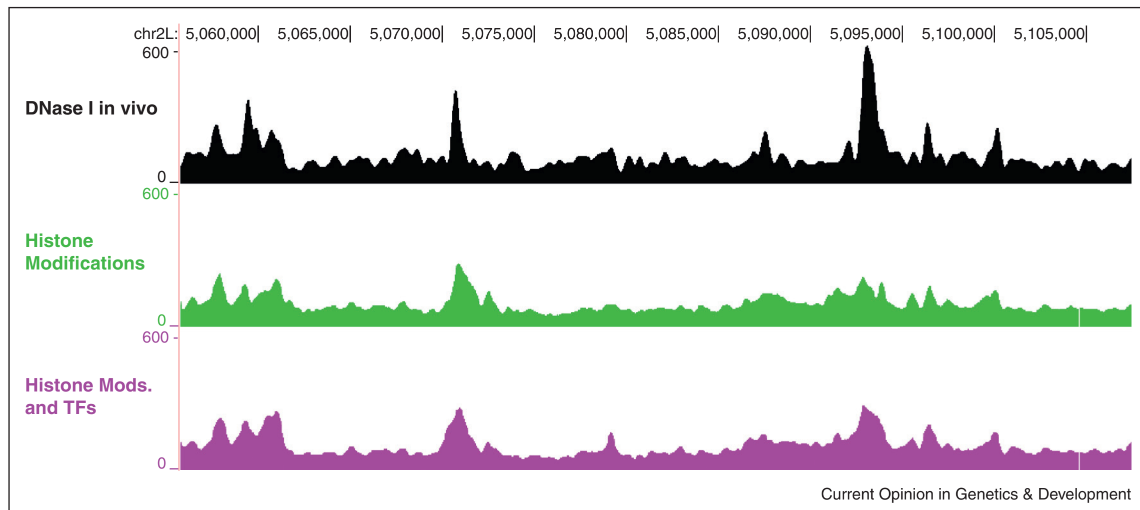
Early studies revealed that TF bound DNA and DNase I sensitivity co-occurred at candidate promoters [5,15]; however, these measurements did not resolve the causality of either event. Did pre-existing DNase I hypersensitivity permit TF binding or did TF binding affect the local chromatin environment? Candidate gene analyses have shown that accessible chromatin correlated with inducibly bound TF binding sites for several factors [16,17,18••]. To test whether accessible chromatin was necessary and sufficient to direct TF binding to consensus elements, genomic assays were needed to examine the comprehensive set of bound target elements and unbound consensus elements. The recent advent of molecular genomics approaches that measure both the accessibility of DNA (DNase-seq, FAIRE-seq, and ChIP-seq) [19–21] and the inducible binding of transcription factors (ChIP-seq) [10••,12••,22,23] allows this causality to be addressed in a comprehensive manner.

Genomic assays reveal that active chromatin is required for TF binding

The first genome-wide study looking at histone marks and inducible TF binding indicated that active chromatin marks preceded TF binding [24]. The authors found that STAT1 binding sites were marked by H3K4 methylation before interferon-induced STAT1 binding [24]. These data suggested that an active chromatin state is necessary for inducible binding. However, it remained unclear if potential, but unoccupied, STAT1 binding sites also harbored active marks, but remained unbound after stimulation.

To test whether or not potential binding sites in active chromatin remain untargeted, we directly compared the chromatin landscape (histone modification and chromatin

Figure 1



DNase I intensity can be modeled using histone marks and TF binding data. DNase I hypersensitivity landscape is inferred by models that use histone modification profiles and TF profiles. Incorporating non-histone chromatin-bound factors into the model increases accuracy, which is consistent with the role of TFs having an additive effect upon DNase I hypersensitivity [5,12••].

associated factors) at inducibly bound, heat shock factor (HSF) DNA elements (HSEs) to unoccupied HSEs [10••]. We found that inducibly bound HSEs resided in chromatin characterized by histone acetylation and H3K4 methylation and unbound HSEs lacked these histone marks (Figure 2). A similar study showed that the glucocorticoid receptor (GR) specifically binds to target elements that are pre-marked by DNase I hypersensitive signal before ligand treatment [12••]. Taken together, these data indicate that TFs are specifically targeted to consensus elements within a region of active chromatin.

The previously mentioned studies were performed in cell lines with an inducing agent (interferon, hormone, and heat stress), but defining the temporal order of chromatin structural change and TF binding is more difficult within a developing organism. Multiple cell types can confound the quantitative analysis of both TF binding and chromatin structure. Additionally, the analysis requires capturing cells at a stage just before detectable TF binding, which is difficult to accomplish in a manner that does not perturb the developmental process [25,26]. To overcome these limitations and study the context-dependent manner of transcription factor binding in erythroid differentiation, Wu *et al.* generated an inducible GATA1 cell line [27•]. They found that erythroid progenitors lacking GATA1 retain the chromatin state (H3K4 methylation and DNase I sensitivity) that is permissive for binding [27•]. Others have captured the early events in the reprogramming of differentiated cells to induced pluripotent stem cells (iPSC) using an assay that allows for cells to be distinguished by their number of cell divisions [28]. Reprogramming is initiated by ectopic expression of Oct4, Sox2, Klf4, and c-Myc, and the authors showed that the primary targets of these factors pre-exist in an accessible state [28].

A special class of TFs termed 'pioneer factors' are often the first detectable transcription factors binding a region of chromatin *in vivo* and can access nucleosomal DNA *in vitro* [29]. Recent genomic studies have shown that H3K4 methylation and DNase I sensitivity precedes binding of the pioneer factors FoxA1 and GATA1 [18••,27•,30]. FoxA1's high affinity for nucleosomal DNA [29] likely allows FoxA1 to bind to transiently accessible chromatin that may be inaccessible to other factors (reviewed in [31]), but the *in vivo* evidence suggests that these sites are not heterochromatic. Here we use 'heterochromatic' to refer to the annotation of chromatin states defined by the presence and absence of specific chromatin marks that likely result in higher order chromatin structure [11,13]. FoxA1 and other TFs are defined as pioneers, because they precede binding of other TFs. These studies indicate that the mechanism and function of pioneer factor binding is not appreciably different from TFs that are not considered pioneers: both classes bind to relatively decondensed chromatin marked by active histone marks and subsequently reinforce and expand the accessible region [10••,12••,32].

We propose that many factors have the potential to pioneer a region. For instance, AP1 binding precedes GR binding and maintains accessible chromatin at over 70% of GR binding sites, but it seems that GR is acting as

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