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## **The conundrum of the functional relationship between transcription factors and chromatin**

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#### **CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

## **The conundrum of the functional relationship between transcription factors and chromatin**

Chromatin has long been defined as a non-inert template for transcription factor (TF) activities. The prevailing view has been that DNA association with histones in chromatin constitutes a general brake to TF-driven activities. Knowledge of chromatin organization and of TF engagement within such chromatin landscapes has been boosted in the last decade by technological breakthroughs in several areas including high-throughput sequencing and high-resolution imaging. Our current refined understanding of transcriptional regulation, while confirming the key influence of chromatin and epigenome on TF activities, has also indicated that general rules dictating the chromatin/TF relationship may lie in continuums of functional interdependencies. Here, we discuss the concept that TFs and chromatin should be thought of as dancing partners harmoniously and constantly adapting to each other rather than being considered as opposed entities.

### **A love affair between TFs and chromatin**

All kingdoms of life possess proteins that impinge on the conformation of DNA and make it fit into the cell or cell nucleus. In eukaryotes, DNA wrapping around nucleosomal histones defines the elementary structure of chromatin, which can further compact DNA through higher-order three-dimensional folding [1]. Consequently, chromatin generates an inherent barrier for DNA-based processes including interaction with TFs. This has spread the commonly accepted dogma that transcriptional regulation by TFs first requires them to act on chromatin to get access to regulatory DNA elements [2]. This prevailing view has however generally undermined indications that chromatin organization itself is leveraged by cells of complex organisms to establish cell-specific transcriptomes. From this perspective, chromatin has offered novel opportunities for complex spatiotemporal gene regulation by TFs in higher eukaryotes. This consideration is of tremendous importance considering that an increase in the complexity of transcriptional regulatory events, rather than in genome size or gene number, is to be considered as the main driver of increased living organism complexity during

evolution [3]. Hence, time has come to consider more systematically TFs and chromatin as co-evolving entities allowing to drive complex transcriptomes.

### **Mutual influence between TFs and chromatin as the key rule driving transcriptional regulatory events**

The role exerted by chromatin in the establishment and maintenance of cell identity is well recognized. In particular, how formation of condensed heterochromatin regions is involved in gene silencing has been the focus of intense research [4]. Even in more relaxed chromatin domains of the euchromatin, it is well established that RNA polymerases need nucleosome free regions (NFRs) to initiate transcription. These NFRs are established by TFs, through intrinsic or cofactor-associated chromatin remodeling activities [2], defining a TF-specific potential to alleviate chromatin-based constraints required to induce gene expression. However, recent studies describing different modes of TF engagement within chromatin indicate that nucleosomes do not systematically act as barriers. For instance, TF binding sites can adopt conformations, when associated with histones, that stabilize TF association. This is true for instance for the high mobility group (HMG) protein SOX2 that binds its motif more stably when in the dyad DNA of a nucleosome than in naked DNA [5]. Other nucleosomal positionings of the SOX2 motif reduce interaction, but this can be overcome by nucleosome binding proteins such as PARP-1 [6] that controls SOX2 binding at nucleosome-bound enhancers whereas binding of SOX2 at nucleosome-depleted enhancers is independent of PARP-1 [7]. Nucleosomal DNA binding by so called “pioneer” or “super pioneer” factors like SOX2, KLF4 or FOXA1 [8, 9] allows chromatin to instruct TF recruitment and induction of gene expression during differentiation. Indeed, once recruited, “pioneer” factors trigger chromatin remodeling to facilitate binding of additional TFs which will themselves further remodel the local chromatin environment and instruct cell-specific transcriptomes in differentiated cells [9]. Hence, TFs and chromatin functional connections most probably involve continuous feedforward loops, a conserved system-level organization in living cells and organisms [10]. Following initial disputed views, the interdependent functional relationship with TFs is also considered nowadays as the rule when transcriptional regulation is analyzed at the level of

the three-dimensional chromatin organization [11, 12], i.e. gene regulation involves mutual influences between chromatin folding and TF recruitment. Therefore, even if a hierarchy exists in the functional connection between TFs and chromatin, the high level of intricacy in their bidirectional connection is often difficult to grasp. In this context, a continuum of TF functional potentialities most probably exists which needs to be better characterized. This will avoid inappropriate usage of current terminology such as calling “pioneer” factor any TF able to remodel chromatin without consideration for its ability to bind nucleosomal DNA in condensed chromatin. Based on the aforementioned considerations, we envision bidirectional influences between TFs and the chromatin have been evolutionary selected in eukaryotes as a mean to increase the potential for complex and diverse transcriptomic regulations.

#### **Understanding context-specific TF activities as a pre-requisite to refining rules of chromatin-based transcriptional regulation**

In addition to TFs being diverse in their functional relationship with the chromatin, in-depth analyses of specific TFs have also shown that a given TF does not uniformly interact with chromatin at all bound regulatory elements. This indicates that better understanding the context-specific functional relationship between TFs and chromatin will be required despite being technically challenging. A more reliable picture of TF-chromatin functional connection will involve better defining how the motif grammar, nucleosome positioning and chromatin folding locally influence TF recruitment and activities in space and time. Related to this is the crucial need to improve our understanding of how multiple TFs work together at regulatory elements [13, 14]. Indeed, single molecule footprinting assays have indicated that co-occupancy of enhancers by several TFs increases nucleosome depletion and suggested that accessible DNA more than motif orientation and physical interaction of TFs dictates how numerous TFs stably engage enhancers in a cooperative manner [14]. However, how much individual TFs contribute to gene expression regulation is highly variable and discriminating between non-functional opportunistic TF binding versus readily functional TF recruitment at different regulatory sites has unfortunately remained difficult and controversial [15-17]. We envision that further technological developments and pluridisciplinary approaches involving genome editing, single-cell and

single molecule analyses, high sensitivity mass-spectrometry together with machine-learning approaches should allow to overcome some of the long-standing limitations which have hindered our understanding of the TF-chromatin functional interactions.

Overall, in our view, TFs and chromatin should now be considered as a single co-evolving entity, which allows to provide the ground for establishment of highly complex and diverse transcriptional programs. While necessary for the understanding of biological systems, the characterization of extreme behaviors that functionally link TFs and chromatin in some instances should not hinder the scientific community to now fully embrace the idea that a delicate and context-specific bidirectional dialogue is the main rule. As such, TFs and chromatin are very much to be considered as full partners and not as two entities trying to cope with one another.

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