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The ubiquitous transcription factor CTCF promotes lineage-specific epigenomic remodeling and establishment of transcriptional networks driving cell differentiation

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Cell differentiation relies on tissue-specific transcription factors (TFs) that cooperate to establish unique transcriptomes and phenotypes. However, the role of ubiquitous TFs in these processes remains poorly defined. Recently, we have shown that the CCCTC-binding factor (CTCF) is required for adipocyte differentiation through epigenomic remodelling of adipose tissue-specific enhancers and transcriptional activation of Peroxisome proliferator-activated receptor gamma (PPARG), the main driver of the adipogenic program (PPARG), and its target genes. Here, we discuss how these findings, together with the recent literature, illuminate a functional role for ubiquitous TFs in lineage-determining transcriptional networks.

Keywords: CCCTC-binding factor (CTCF), cell differentiation, cistrome, DNA hydroxymethylation, epigenome, enhancer, TET methylcytosine dioxygenase, transcriptome, ubiquitous transcription factor

Abbreviations: CTCF, CCCTC-binding factor; KLF, Krüppel-like factors; PPARG, Peroxisome proliferator-activated receptor gamma; CEBP, CCAAT/enhancer binding protein; H3K4me1, monomethylation of histone H3 lysine 4; H3K27ac, acetylation of histone H3 lysine 27; TET, Ten-eleven translocation methylcytosine dioxygenase; TF, Transcription factor; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine.

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Extra View

A dynamic CTCF chromatin binding landscape promotes DNA hydroxymethylation and transcriptional induction of adipocyte differentiation.

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Transcriptional Control of Cell Differentiation

Cell differentiation is a highly dynamic process, which allows the establishment of defined phenotypes. This is accomplished through specification of unique transcriptomes, a process that heavily relies on usage of cell type-specific enhancers.[1,2] Enhancer activation can be achieved through sequential TF recruitment to the chromatin following initial binding of pioneer TFs or involve a concomitant and cooperative binding of multiple TFs.[3-5] Cooperative binding may involve assisted loading where TF binding to close or overlapping motifs may facilitate each other's binding because of the very dynamic nature of TF-chromatin interactions.[6,7] Either way, enhancer activation requires chromatin/epigenomic remodelling, which has now been widely used as a surrogate to monitor enhancer activities during cell differentiation, including adipocyte differentiation.[8-10] In this context, we have contributed to the identification of DNA methylation as a novel epigenetic mark actively controlled by TFs at enhancers.[11,12] Moreover, using adipocyte differentiation as a model system, we have shown that loss of DNA methylation at activated enhancers is reciprocally linked to a gain in DNA hydroxymethylation (**Fig. 1**).[13,14] The mechanistic connection between these observations is underlined by Ten-eleven translocation methylcytosine dioxygenase (TET)-mediated DNA hydroxymethylation being an intermediate in the DNA demethylation process.[15] Importantly, a recent study functionally linked DNA hydroxymethylation to DNA demethylation, enhancer activation and gene induction during cell differentiation.[16] However, DNA hydroxymethylation is relatively stable[17] and can also modulate TF or chromatin modifier DNA recognition[18] suggesting that cytosine hydroxymethylation may represent a novel epigenetic mark *per se*.[19] Fujiki et al. subsequently ascribed to the adipocyte lineage-determining TF Peroxisome proliferator-activated receptor gamma (PPARG) the function of promoting DNA hydroxymethylation through chromatin recruitment of TET.[20]

In addition to lineage-determining factors such as PPARG, which are expressed in specific tissues, the TF repertoire

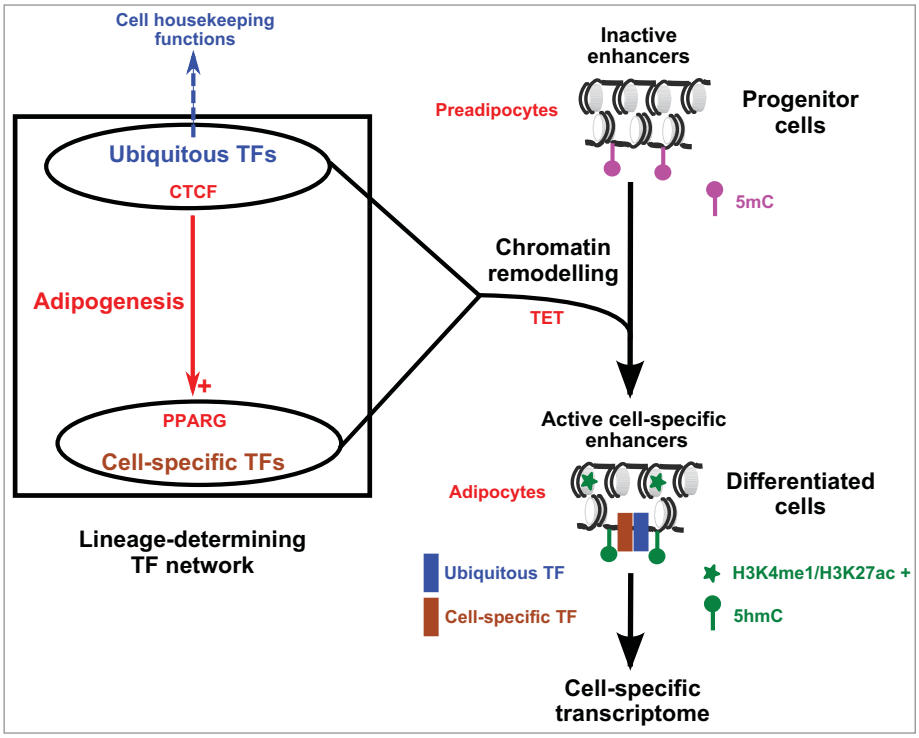

Figure 1. Involvement of ubiquitous TFs in the transcriptional regulation of cell differentiation. The main concepts discussed in the manuscript are summarized (see text for details). The absence or presence of histone modifications that characterize active enhancers (H3K4me1 and H3K27ac) is indicated together with DNA methylation (5mC) and DNA hydroxymethylation (5hmC). H3K4me1, monomethylation of histone H3 lysine 4; H3K27ac, acetylation of histone H3 lysine 27; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine.

comprises ubiquitous TFs with similar expression in almost all tissues.[21] However, with the exception of general TFs involved in the pre-initiation complex (PIC), the role of ubiquitous TFs in cell differentiation has long remained elusive. Here, we discuss the general implications for our most recent findings showing a requirement for ubiquitous CCCTC-binding factor (CTCF) in defining the adipocyte-specific epigenome and transcriptome (**Fig. 1**).[22]

CTCF As a Driver of Cell Type-Specific Enhancer Activities

CTCF, initially identified as a TF binding to insulators,[23] was latter revealed to harbour pleiotropic activities including transcriptional activator/repressor, nucleosome positioning and chromatin 3-dimensional organizer activities.[2,23,24] Based on this latter function and on the identification of conserved CTCF binding events across various cell-types and tissues,[25-27] this TF was proposed to fulfil a general chromatin organization role.[28] At the same time, specific roles for CTCF in neuronal and haematopoietic cell differentiation had been defined.[29] In this context, detailed analyses of CTCF cistromic studies revealed the existence of cell type-specific chromatin binding sites.[30] Indeed, thorough comparison of the CTCF binding landscape in 19 human cell-types revealed that 64% of identified CTCF binding sites are not conserved.[30] This may have been previously overlooked owing to a more limited number of analyzed cell types or to the use of stringent criteria to call bound regions. Indeed, conserved binding sites show stronger CTCF recruitment and show less degenerate CTCF binding motifs compared to cell type-specific CTCF bound regions.[22,30,31] We have now shown that the CTCF cistrome is highly dynamic during the course of adipogenesis since we found that more than half of the CTCF binding sites (>30,000 sites) identified across 4 stages of the differentiation process were not constitutively bound.[22] Moreover, our study provides evidence that this dynamic CTCF chromatin binding occurs at lineage-specific enhancers, which promote adipocyte differentiation (**Fig. 1**).[22] CTCF binding at these enhancers is not detected in preadipocytes and occurs upon differentiation when these regulatory sites are activated. As discussed hereafter, CTCF is necessary for DNA hydroxymethylation[22] of enhancers, a process required for cell differentiation.[16,20] Interestingly, another recent study has uncovered a similar role for another ubiquitous TF, the NF-Y complex, in activation of cell type-specific enhancers.[32] How these ubiquitous TFs are targeted to cell type-specific regulatory sites remains to be defined. Regarding CTCF, post-translational modifications and the existence of different modes of DNA recognition might help to modulate target sequence recognition.[33,34] Alternatively, combinatorial TF binding to enhancers, which now arises as a prevalent mechanism, could shape the CTCF cistrome. Direct CTCF interaction with TFs may, for instance, be involved in this process.[23,35] Of note, differentially active enhancers in mast cell and multipotent haematopoietic progenitors require TFs which are both specific and shared between the 2 cell-types to regulate transcription, further indicating that commonly expressed TFs are instrumental in regulating cell type-specific enhancer activities.[27,36]

Involvement of CTCF in Chromatin Remodelling at Cell Type-Specific Enhancers

Multiple mechanisms may explain the requirement for combinatorial TF binding to enhancers. For instance, combinatorial TF binding to enhancers during adipocyte differentiation allows for cooperative coactivator recruitment and induction of histone acetylation.[5] In this context, in addition to PPARG, we have found that CTCF promotes TET-mediated DNA hydroxymethylation of

enhancers driving adipocyte differentiation.[22] In addition to such "quantitative" effects where multiple TFs cooperate to reinforce or amplify a given chromatin modification, individual contributions of different TFs to different enhancer functionalities may occur. TF binding to enhancers is not always simultaneous and can rather involve different kinetics implying a sequential or even a mutually exclusive recruitment.[5,37] This may in part be driven by the cyclic nature of transcriptional regulatory events that require instructed and sequential TF/cofactor chromatin binding and dissmisal.[38,39] In this context, it will be of great interest to better define whether and how the different functionalities of CTCF on the chromatin structure are involved at enhancers and how they relate to those of collaborating TFs. Indeed, CTCF is able to control local epigenetic modifications of DNA and histones.[22,40] It is also able to position surrounding nucleosomes[24] and to act on chromatin 3-dimentional folding[41]. Regarding NF-Y, it was hypothesized that this factor promotes chromatin opening at enhancers (potentially through nucleosome displacement) to favor recruitment of master lineage-determining TFs.[32]

An important aspect of this research area will be to better define the relative influence of DNA methylation/hydroxymethylation on chromatin binding of ubiquitous and cell-specific TF. For instance, CTCF DNA binding can be inhibited by DNA methylation[36] while, reciprocally, CTCF is able to promote DNA demethylation suggesting a mutual influence.[12,35,42] Importantly, this relationship may be strongly linked to the genomic environnment as, for example, convertion of methylated DNA into hydroxymethylated DNA correlates with CTCF binding mostly outside of CpG islands (CGIs).[43]

Finally, cell-specific CTCF binding has been shown to influence chromatin looping to promote interaction between *Ubx* enhancers and promoter to trigger gene transcriptional activation in *Drosophila*.[41]

Therefore, CTCF emerges as a crucial chromatin remodeler at cell-type specific enhancers.

Ubiquitous TFs and Lineage-Determining TF Networks

We identified the adipose lineage-determining factor PPARG as one main target gene dynamically bound and transcriptionally regulated by CTCF during adipocyte differentiation, (**Fig. 1**).[22] Reminiscent of the establishment of specialized transcriptomes in other cell types such as hepatocytes,[44] adipocyte differentiation involves the build-up of a TF network, which includes, in addition to PPARG, members of the Krüppel-like factor (KLF) and CCAAT/enhancer binding protein (CEBP) families. These TFs show cross-regulation of their expression and cooperate to regulate important adipose-specific target genes.[45,46] Our study therefore shows that CTCF is part of this network through the regulation of both PPARG expression and activities (**Fig. 1**). These findings are reminiscent of those of Delgado-Olguín et al. regarding myogenesis during which CTCF both regulates the expression of, and cooperates with MyoD [47]. These studies functionally validate predictions made from the analyses of DNAseI footprints from 41 cell and tissue-types indicating that CTCF was surprisingly involved in most cell type-specific TF networks. Interestingly, a similar prediction was made for additional ubiquitous TFs including SP1, NFYA, and MAX suggesting that this could be a general organization scheme of lineage-determining transcriptional networks.[48]

Concluding Remarks

Our recent study provides an important new contribution to the recent litterature describing how ubiquitously expressed TFs functionally contribute to establishing cell-specific transcriptomes and phenotypes. However, important questions still remain to be answered. For instance, CTCF is characterized by an uncommonly large number of potential activities when bound to chromatin, making it central to the regulation of the functional genomic landscape. However, a major challenge arising is to better understand how CTCF's multiple functionalities are specified in space and time. With this aim, it will be instrumental to better understand how cues provided by the local chromatin environment and collaborating TF/cofactors allow for region and cell-specific CTCF binding and functions. This will undoubtly significantly improve our understanding of the functional connection between ubiquitous and cell type-specific TFs in lineage-determining transcriptional networks.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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