Review

Transcriptional regulation by coactivators in embryonic stem cells

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Embryonic stem (ES) cells, like all cell types, are defined by their unique transcriptional signatures. The ability of ES cells to self-renew or exit the pluripotent state and enter differentiation requires extensive changes in their transcriptome and epigenome. Remarkably, transcriptional programs governing each cell fate must remain sufficiently malleable so that expression of only a handful of transcriptional activators can override the pre-existing state by collaborating with an unexpectedly elaborate collection of coactivators to specify, restrict and stabilize the new state. Here, we discuss recent advances in our understanding of how the same coactivator can interpret multiple lines of information encoded by different activators and integrate signals from diverse regulators into stem cell-specific transcriptional outputs.

Functional interplay between activators and coactivators in embryonic stem cells

ES cells are highly specialized cells with an unmatched ability to faithfully propagate themselves indefinitely (self-renewal) while retaining the capacity to undergo differentiation to generate every cell type in the body (pluripotency). During these processes, concerted, sweeping changes that involve the degradation, synthesis and reorganization of transcription factors and their cofactors must occur to direct the rapid reprogramming of gene expression networks, remodeling and stabilization of the new transcriptional landscape.

The expression of only a handful of sequence-specific DNA-binding transcription factors is restricted to the pluripotent state (e.g. OCT4, NANOG), whereas most of the transcription factors that have been implicated in stem cell maintenance are expressed in many other cell types (e.g. SOX2, KLF4, c-MYC, SMADs, STATs). How do ES cells utilize a limited number of cell type-specific transcription factors to define a stem cell-specific transcriptional signature? Although the combinatorial assembly of transcription factors directed by OCT4 on gene promoters offers some degree of specificity [1,2], their ability to recruit a wide array of cofactors adds the necessary breadth and flexibility in their transcriptional repertoire to accommodate a wide range of transcriptional responses in ES cells.

Transcriptional cofactors are a large class of loosely grouped protein and multi-subunit protein complexes that regulate gene expression through diverse mechanisms. OCT4 and SOX2 recruit histone modifiers (e.g. p300/CBP [3], the WDR5/trithorax complex [4]) and chromatin remodelers (e.g. esBAF [5]) to ensure active loci are maintained. Independent of chromatin, they also cooperate with multi-subunit Mediator [6], TAFs/TFIID [7] and, unexpectedly, the nucleotide excision repair (NER) complex containing XPC, RAD23B and Centrin 2 (SCC [7]) to execute stem cell-specific transcriptional programs (Glossary and Figure 1).

It is worth noting, however, that many, if not all, of these cofactors are also involved in transcriptional activation in cell types other than ES cells. Therefore, the challenge is to elucidate how this expansive but rather universal set of coregulators can coordinate diverse transcriptional outputs that must be precisely tuned in a cell type-specific manner. The multi-subunit nature of many of these cofactors and variations in the subunit composition provide unique contact surfaces for select transcription factors. The ability of cofactors (e.g. Mediator) to adopt distinct conformations induced by different activators permits specific activator-dependent readouts sensed by the transcription apparatus

Glossary

Chromatin remodeler: an ATP-dependent protein complex that disrupts and reforms histone–DNA contacts to facilitate nucleosome shifting along a piece of DNA, reorient DNA around histone octamers, position nucleosomes on the DNA, and/or exchange histones.
General transcription factors: an evolutionarily conserved set of protein or protein complexes (TFIIA, B, D, E, F and H) that, together with RNA polymerase II, form the pre-initiation complex (PIC) that is responsible for the transcription of almost all eukaryotic mRNA and miRNA genes.
Histone modifier: protein or protein complex that deposits or removes post-translational modifications on histone cores and/or tails. Known modifications of histones include methylation, acetylation, phosphorylation, ubiquitination, SUMOylation, citrullination, glycosylation, propionylation, butyrylation, proline *cis–trans* isomerization, ADP-ribosylation, and proteolysis.
Plant homeo domain (PHD) finger domain: a zinc-coordinating domain of 50–80 amino acids that anchors PHD-containing proteins to unmodified or various forms of modified lysines on the histone H3 tail (H3K4me3, H3K9me3, H3K4me0).
Sequence-specific transcription factor: a protein that recognizes and binds a specific DNA motif in the promoter and/or enhancer region of a given gene, and can mediate gene activation or repression.
Transcriptional cofactor: a protein or protein complex that mediates transcriptional activation or repression via interaction with general and/or sequence-specific transcription factors.
Transcriptional coactivator: a transcriptional cofactor that enhances transcription of a target gene.
Transcriptional corepressor: a transcriptional cofactor that represses transcription of a target gene.

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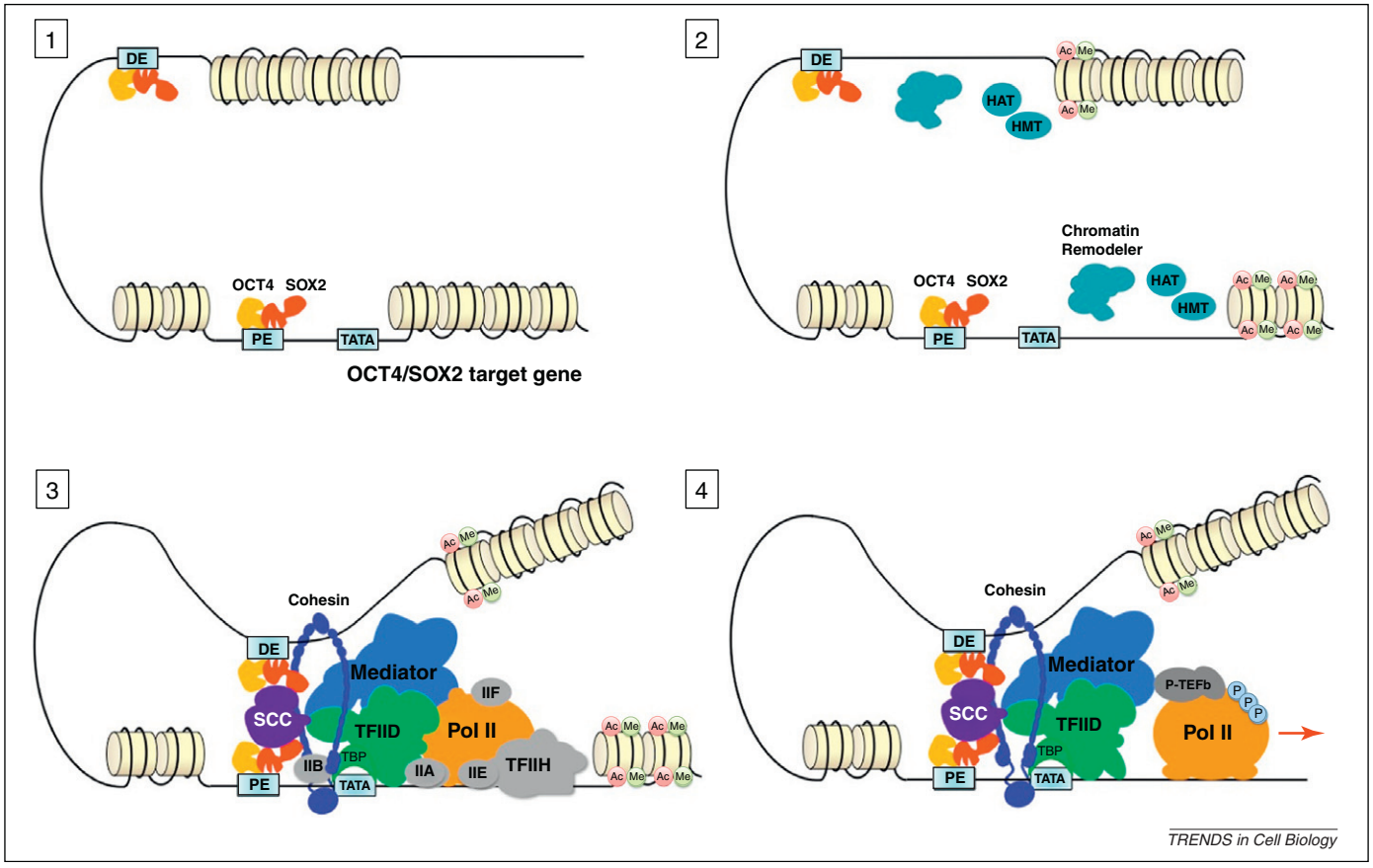

Figure 1. Multistep activation model of an OCT4/SOX2 target gene in embryonic stem cells. The transcription apparatus is assembled on an OCT4/SOX2 target gene promoter in a spatially and temporally regulated manner to initiate gene expression. The stepwise assembly is depicted here in the order proposed in [68]. (**1**) 'Orchestration': sequence-specific transcription factors, OCT4 and SOX2, bind to both the proximal (PE) and distal (DE) enhancers. (**2**) 'Access': chromatin remodelers and histone modifying enzymes such as histone acetyltransferases (HATs) and histone methyltransferases (HMTs) act coordinately to remodel chromatin around the gene loci by altering nucleosome positioning and histone modifications. This allows access by other transcription factors and cofactors to the gene promoter. (**3**) 'Initiation': pre-initiation complex (PIC) and various coactivators (e.g. TAFs/TFIID, Mediator, SCC) are assembled onto the core promoter via interaction with activators bound on PE and DE (e.g. TAF–OCT4/SOX2 or SCC–OCT4/SOX2), promoter DNA elements (e.g. TBP–TATA) and modified nucleosomes (e.g. TAF3–H3K4me3). DNA looping by cohesin and Mediator can further stabilize the long-range enhancer–promoter DNA interaction. (**4**) 'Elongation': phosphorylation of the C-terminal domain (CTD) of the largest subunit of RNA polymerase II (Pol II) by TFIIH facilitates promoter escape, whereas subsequent phosphorylation by P-TEFb stimulates the transition of Pol II into productive elongation.

[8]. Furthermore, multi-subunit coactivator complexes often comprise functional submodules that allow them to participate in various facets of transcriptional regulation and, in some cases, processes beyond transcription. In ES cells, for example, using a DNA repair complex as a transcriptional coactivator for OCT4 and SOX2 represents yet another strategy to further diversify their transcriptional repertoire by coordinating with other cellular processes.

In this review, we focus on the roles of TAFs, Mediator, and the XPC/SCC complex in stem cell-specific gene activation. Although they represent only part of the known transcriptional network in ES cells, they highlight a recurring theme in cell-type specific transcriptional control: functional diversity, structural flexibility and compositional changes give coactivators an unprecedented ability to interact and coordinate with a wide array of transcription factors and cofactors to execute stem cell-specific gene regulatory programs (Figure 2).

TAFs

The recruitment of transcription factor TFIID to protein-coding gene promoters represents a defining step in the ordered assembly of the general transcription factors (GTFs) into a functional pre-initiation complex (PIC) that culminates in initiation of transcription [9] (Figure 1). TFIID is a multiprotein complex comprising the TATA binding protein (TBP) and 13 or 14 TBP-associated factors (TAFs). TAFs are an eclectic collection of proteins that possess enzymatic activity, recognize core promoter elements, anchor TFIID to nucleosomes and function as transcriptional coactivators [9–11]. Given the multitude of essential protein–protein and protein–DNA transactions that TFIID mediates, the composition of TFIID has traditionally been thought to be invariant. However, with the discovery of tissue-specific TAFs, TAF paralogs and TBP-related factors (TRFs) came the appreciation that TFIID is as capable as any other coactivator of imparting gene selectivity and functional flexibility to the PIC [9,12] (Figure 2a).

TFIID levels tend to be elevated in highly proliferative cell types (e.g. cancer cells, ES cells) and are downregulated in terminally differentiated cells (e.g. muscle cells, adult hepatocytes) [9,13]. This is consistent with the observation that transcription of cell cycle genes often requires TFIID [14]. Therefore, it can be difficult to decipher the role of TAFs in ES cells; that is, to separate the stem cell-specific functions of TAFs/TFIID from their general role in proliferation. Nevertheless, several unbiased