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Message in a nucleus: signaling to the transcriptional machinery

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Tissue differentiation and signal transduction involve dramatic changes in gene expression. These changes can be brought about by the expression or activation of sequence-specific transcription factors. In order to regulate their target genes, such factors must navigate the intricate chromatin environment and engage the complex basal transcriptional machinery. We discuss three mechanisms through which signaling pathways can interact with complexes that alter chromatin structure or recruit RNA polymerase II. Signals that promote differentiation may alter the properties of such transcriptional regulatory complexes by incorporating tissue-specific subunits. Alternatively, adaptor subunits specialized to interact with specific transcription factors may allow a single complex to respond to multiple signals. Finally, individual regulatory proteins may integrate a variety of signals, allowing crosstalk between pathways.

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Introduction

Developmental signals induce programs of gene expression that lead to the differentiation of a diverse array of cell types and tissues. A precise interplay between *cis*-acting elements and *trans*-acting factors allows signaling pathways to activate or repress the expression of specific genes and to maintain these expression patterns in differentiated tissues. Transcription initiation represents a key regulatory step in this process. It requires the directed assembly of a pre-initiation complex, consisting of general transcription factors (GTFs) and RNA polymerase II (pol II), on a core promoter. Sequence-specific DNA-binding proteins bound to enhancer regions assist the assembly and function of this pre-initiation complex by facilitating the recruitment of multisubunit regulatory complexes. These complexes may remodel chromatin, modify histones, or directly recruit the basal transcriptional machinery [1,2]. Recent studies have described a variety of mechanisms by which signaling pathways interact with GTFs and regulatory complexes. These interactions may also allow crosstalk between different signaling pathways at the level of target gene regulation in the nucleus.

In addition to pol II, the basal transcriptional machinery consists of a group of GTFs (TFIIA, B, D, E, F, and H) that assemble on the core promoter, position pol II on the start site and trigger mRNA synthesis [3]. Recognition of the core promoter DNA sequence by TFIID is mediated by TATA-binding protein (TBP) and its associated factors (TAFs), which can also interact with sequence-specific activators [3]. Metazoans have evolved multiple TFIID-related complexes specific for particular cell types or promoter sequences, adding another level of complexity to transcriptional regulation [4]. One type of regulatory complex, the multisubunit Mediator complex, directly binds pol II and other GTFs and can recruit them to target promoters, as well as contributing to transcriptional initiation downstream of pol II recruitment [5]. The Mediator complex is brought to the promoter region by interactions with sequence-specific transcription factors through a variety of adaptor subunits [6].

Eukaryotic DNA is packaged into nucleosomes and higher order chromatin structures that have a repressive effect on transcription. Heterochromatin assembly can maintain genes in a stably repressed state, but even in euchromatic regions nucleosomes may interfere with DNA sequence recognition by transcription factors and with the binding or progression of pol II. Two classes of transcriptional regulatory complexes act by changing chromatin structure. ATP-dependent chromatin-remodeling complexes alter the pattern of contacts between DNA and histones to expose DNA sequences that would otherwise be occluded by nucleosomes. This can be accomplished by nucleosome sliding, DNA bulging, nucleosome eviction, or changing the structure of the nucleosome by incorporation of histone variants [7]. The core ATPase subunit of each chromatin-remodeling complex determines its mechanism of action [8], while a variety of accessory subunits have functions that are less well understood.

Histone-modifying complexes alter chromatin structure by covalently modifying specific amino acids in the histone tails. These modifications may directly influence chromatin compaction, or may create docking sites for specific proteins that include chromatin-remodeling proteins, GTFs, heterochromatin proteins, and other

Glossary

BAF: BRG1-associated or hBRM-associated factors. A chromatin-remodeling complex of the SWI/SNF family, containing the BAF250 subunit.
CBP: (cAMP-response element-binding protein, CREB) binding protein. A commonly used histone acetyltransferase.
CHD8: Chromodomain protein 8. An ATP-dependent chromatin-remodeling protein.
GTFs: General transcription factors. A term used to describe TFIIA, TFIIB, TFIIC, TFIID, TFIIE, TFIIF, and TFIIH.
HAT: Histone acetyltransferase. A complex that acetylates lysines in histone tails, promoting transcriptional activation.
NURF: Nucleosome-remodeling factor. A chromatin-remodeling complex that uses the ISWI ATPase subunit.
PBAF: Polybromo-associated BAF. A complex identical to BAF except that it contains BAF180 and BAF200 instead of BAF250.
pol II: RNA polymerase II. The primary RNA polymerase for protein-coding mRNAs. Pol I transcribes primarily ribosomal RNA, and pol III transfer RNA and other non-coding RNAs.
STAGA: Spt3-TAF9-GCN5L acetylase. A histone acetyltransferase complex.
SWI/SNF: Switching defective and sucrose non-fermenting. A chromatin-remodeling complex first identified in yeast through these two phenotypes.
TAFs: TBP-associated factors. A set of proteins that associate with TBP to constitute TFIID.
TBP: TATA-binding protein. The protein within TFIID that recognizes the TATA box within the core promoter.
TFTC: TBP-free TAFII-containing complex. A histone acetyltransferase complex.
Tip60: Tat interactive protein (60 kDa). A histone acetyltransferase complex.
TRF3: TBP-related Factor 3. A protein that can substitute for TBP to recognize a different set of core promoters.
TRRAP: Transformation–transactivation domain-associated protein. A large subunit of several histone acetyltransferase complexes that interacts with activators.

factors [9]. Acetylation of lysines in the histone tails by histone acetyltransferases (HATs) contributes to transcriptional activation, while methylation of lysines or arginines or ubiquitylation of lysines can create marks for either transcriptional activation or repression, depending on the specific residue modified [9]. For instance, the Polycomb group proteins, which maintain a silenced chromatin state on crucial developmental genes, include a histone methyltransferase for lysine 27 of histone H3 as well as a complex (Polycomb Repression Complex 1, PRC1) that recognizes this specific modification [10]. Interestingly, some enzymes initially characterized for their effects on histones can also modify sequence-specific transcription factors, altering their activities and providing a mechanism for feedback [11,12]. Recent studies have begun to elucidate how intercellular signals use this multitude of transcriptional regulatory complexes to establish transcriptional programs during development.

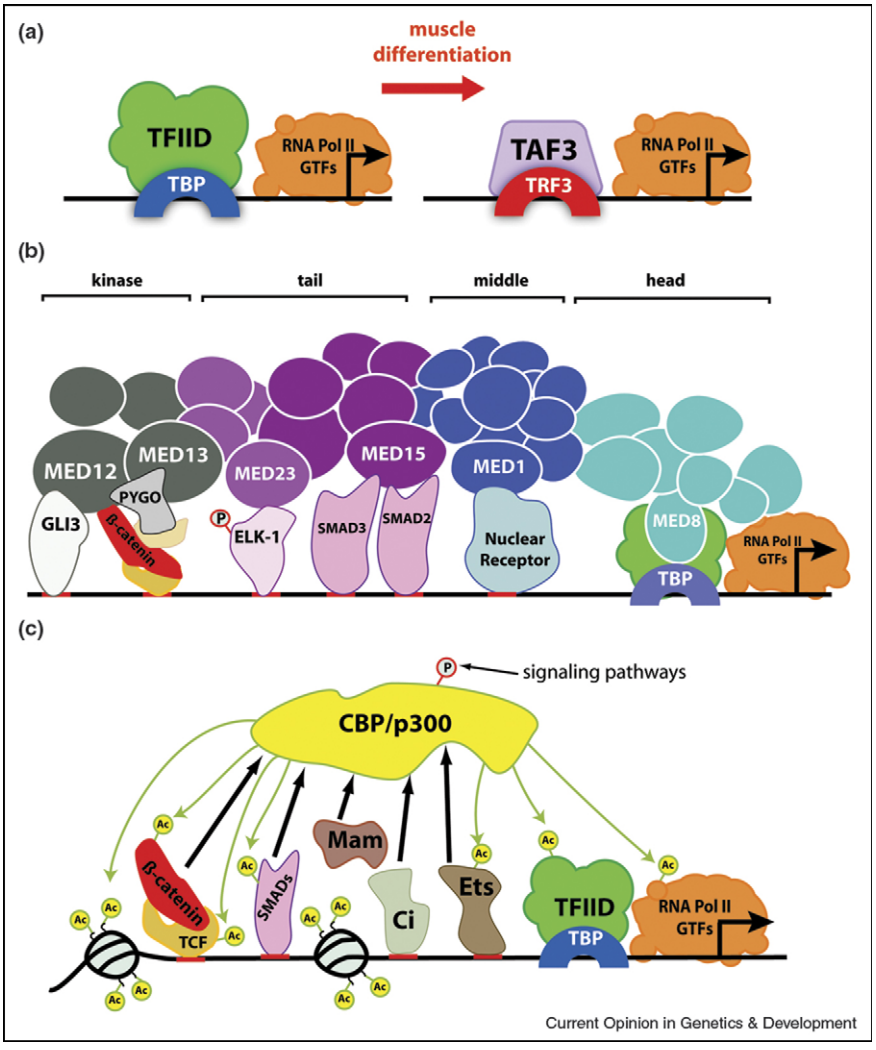
Differentiation-dependent switches in transcriptional regulatory complexes

One mechanism by which signals that lead to cell differentiation can regulate the transcription of multiple genes in a coordinated manner is by altering the cellular transcriptional machinery. A striking example of this strategy is the *Drosophila* testis, in which multiple tissue-specific TAF homologs as well as the TBP-related factor TRF2 are required for the transcription of genes involved in spermatid differentiation [13,14]. These TAFs appear to counteract the repressive effect of the Polycomb complex PRC1 on certain spermatid-specific genes. They do this both by sequestering PRC1 components in the nucleolus, and by recruiting Trithorax, which promotes transcriptional activation by methylating lysine 4 of histone H3 [15•]. In mammals, TAF7L replaces TAF7 and TRF2 replaces TBP late in spermatogenesis [16–18], and TAF4b is required for normal germ cell development in both the testis and ovary [19,20]. The role of TAF4b in ovarian granulosa cells appears to be partially mediated by induction of the transcription factor c-Jun [21]. Interestingly, incorporation of TAF4b enhances the ability of the TFIID complex to recognize the core promoter of *c-jun* and other ovary-specific genes, and alters its conformation so as to increase its accessibility to activators [22•].

An even more dramatic transformation of the core promoter complex occurs when mouse myoblasts differentiate into myotubes: TFIID disappears and is replaced by a smaller complex containing only TAF3 and the TBP homolog TRF3 [23••] (Figure 1A). This substitution may prevent the transcription of genes expressed in undifferentiated cells, as well as allowing the transcription of muscle-specific genes such as *myogenin*. It is not yet clear how transcription of housekeeping genes is maintained following the loss of TFIID, or how the noncoding RNAs transcribed by pol I and pol III are affected. The replacement seems to occur at the transcriptional level and is presumably controlled by myogenic transcription factors, although the precise mechanism has not been determined. TRF3 is also essential for hematopoiesis in zebrafish, suggesting that it may substitute for TBP in additional cell lineages [24].

An analogous switch in a chromatin-remodeling complex occurs during neuronal differentiation in the mouse spinal cord. Two subunits of the SWI/SNF-related chromatin-remodeling complex present in neural progenitor cells, BAF45a and BAF53a, are replaced in differentiating neurons by the BAF45b, BAF45c, and BAF53b isoforms [25••]. This switch is functionally important, since BAF53b has an essential role in activity-dependent dendritic outgrowth that cannot be substituted by BAF53a [26]. BAF53b appears to target the transcription factor Calcium-responsive transactivator (CREST) to the promoters of genes involved in dendritic development [26]. By contrast, overexpression of BAF45a increases the number of proliferating neural progenitor cells and interferes with neuronal differentiation [25••]. Additional mechanisms for wholesale transformation of transcriptomes through changes in the transcription machinery may come to light with further analysis of the transcriptional regulatory

Figure 1



Mechanisms for interaction between signaling pathways and the general transcriptional machinery. **(A)** Developmental signals that trigger differentiation can result in the replacement of a core transcriptional complex. When myoblasts differentiate into myotubes, TFIID is replaced by a smaller complex containing TAF3 and the TBP homolog TRF3. This complex recognizes the promoters of muscle-specific genes. **(B)** Transcriptional complexes can contain subunits specialized to act as adaptors for signal-regulated transcription factors. The Mediator complex interacts with pol II and GTFs through its head module (turquoise), and with multiple DNA-binding proteins and coactivators through individual adaptor subunits in its middle (blue), tail (purple) and kinase (gray) modules. Only transcription factors regulated by signaling pathways are shown; they are represented on a single enhancer region for convenience, but would in fact recruit the complex to different target genes. **(C)** Some transcriptional regulators can integrate multiple inputs, allowing crosstalk between signaling pathways. The histone acetyltransferase CBP is recruited (black arrows) by a large number of signal-regulated and other transcription factors, again represented on a single hypothetical enhancer. Some of these factors are themselves acetylated by CBP (green arrows). The activity and binding preferences of CBP itself can also be regulated by post-translational modifications controlled by signaling pathways.

complexes that are present in differentiated cell types *in vivo*, rather than in a small number of tissue culture cell lines.

Transcriptional complexes contain subunits dedicated to receiving specific signals

Such dramatic alterations of the transcriptional machinery would be unsuitable for cells that must remain poised to respond to a variety of possible signals by transcribing the appropriate target genes. An alternative strategy requires multiple forms of a transcriptional regulatory complex to coexist in the same cells, where they can respond to different factors. A single complex may also contain multiple subunits specialized to act as adaptors or transducers for specific transcription factors or developmental signals.

The SWI/SNF chromatin-remodeling complex is required for the transcription of many genes through interactions with a variety of transcription factors. In

addition to the subunit isoforms specific to neuronal differentiation described above, two distinct forms of the complex are defined by mutually exclusive but unrelated accessory subunits. In addition to a common set of core subunits, the BAF complex contains the BAF250 subunit, while PBAF instead contains BAF180 and BAF200 [27]. BAF and PBAF coexist in the same cells, but have distinct developmental functions. Two mouse BAF250 isoforms are required for embryonic stem cell maintenance and mesoderm formation, while BAF180 affects the development of the heart and placenta [28–30]. In *Drosophila*, the BAF250 ortholog Osa has important roles early in development, including repressing target genes of Wingless (Wg), a Wnt family signaling protein [31•]. By contrast, the fly homologs of BAF180 and BAF200 are required only at late stages of development [32,71]. These phenotypic differences may reflect recruitment by different sequence-specific transcription factors. BAF250 homologs have been shown to interact directly with the glucocorticoid receptor, Zeste, the GATA transcription factor Pannier, its coactivator Chip, and acidic activators [33–37], while human BAF200 can bind to Serum response factor [38], and BAF180 regulates genes that are targets of the retinoic acid receptor [30]. A third subunit, Supporter of Activation of Yellow Protein (SAYP), specific to the *Drosophila* PBAF complex may interact with additional transcription factors [32]. However, if BAF250, BAF200, and BAF180 were only required to recruit the SWI/SNF complex to a variety of promoters, it is unclear why their presence should be mutually exclusive. Perhaps these accessory subunits also confer distinct chromatin-remodeling properties on the BAF and PBAF complexes.

Several other examples of interactions between subunits of transcriptional regulatory complexes and specific transcription factors downstream of signaling pathways have been described. The nucleosome-remodeling factor (NURF) chromatin-remodeling complex interacts with the ecdysone receptor and with Ken & Barbie, an inhibitor of JAK/STAT target genes, and requires the NURF301 subunit to regulate targets of these transcription factors [39•,40]. Target genes of the Notch signaling pathway are repressed in the absence of Notch signaling by the histone chaperone Anti-silencing function 1 (Asf1), which is recruited through interactions with the Notch-specific corepressor Hairless [41]. Wnt target genes are repressed by a remodeling complex that is recruited at least partly through interactions of the chromodomain protein CHD8/Kismet with β-catenin; this mechanism may limit the maximal activation of these genes by Wnt signaling [42].

The Mediator complex, which is broadly required for both basal and activated transcription by pol II, provides a striking example of a general complex containing multiple specialized subunits. This complex can be divided into head, middle, and tail modules on the basis of electron microscopic visualization and biochemical dissociation studies, and large and small forms of the complex are distinguished by the presence or absence of an additional kinase module consisting of four subunits [43]. The head module is required for interactions with pol II and the general transcription factor TFIIF [44], while the tail module interacts with sequence-specific activators [45]. The middle module contributes to both functions, partly by controlling the conformation of the entire complex [46]. A number of Mediator complex subunits act as adaptors for specific transcription factors regulated by signaling pathways (Figure 1B). MED1 interacts with ligand-bound nuclear receptors [47]; MED15 interacts with Smad2 and Smad3, which transduce TGF-β family signals [48]; and MED23 interacts with Elk-1 that has been phosphorylated by MAP kinase [49•]. MED12 and MED13, subunits of the accessory kinase module, interact with the coactivator Pygopus (Pygo) and with β-catenin to turn on Wingless target genes [50,51], as well as with Gli3, a transcription factor controlled by Sonic hedgehog signaling [52]. Numerous other transcription factors have been shown to interact with the subunits mentioned above and with additional subunits [6]. The Mediator complex thus seems to consist of a core functional unit and a collection of adaptor subunits each able to interact with multiple transcription factors. This organization may be necessary to enable its recruitment to essentially all pol II target genes.

There are intriguing indications that the Mediator complex may itself be functionally regulated by certain signaling pathways. The MED1 subunit is phosphorylated by activated ERK, enhancing its association with the Mediator complex [53•,54]. This phosphorylation can be stimulated by the thyroid and steroid hormones that use MED1 as an adaptor subunit [54]. In yeast, phosphorylation of SRB9/MED13 by PKA enhances its ability to repress the expression of genes induced by nutrient deprivation [55]. Two different transcriptional activators, VP16 and Sterol regulatory element-binding protein (SREBP), have been shown to induce different conformational changes when bound to the Mediator complex [56•], suggesting that binding of one activator could facilitate or inhibit interactions of the complex with another. The Mediator complex can also feed back on transcription factors; for instance, the subunit Cdk8 phosphorylates the intracellular domain of Notch, promoting its degradation [57]. These findings suggest that the Mediator complex is not simply a passive array of adaptors, but may play an active role in signal-regulated transcription.

A single protein can integrate a variety of signaling information

The complexes discussed above contain subunits specialized to receive information from particular signaling

pathways. By contrast, other transcriptional regulators appear to be capable of integrating a broad array of signaling information through a single protein. The histone acetyltransferases (HATs) CREB Binding Protein (CBP) and p300 provide one such example. These molecules are recruited by β-catenin to activate Wnt-mediated transcription, by Smads to activate TGF-β-mediated transcription, by Mastermind (Mam) to activate Notch-mediated transcription, by Cubitus interruptus (Ci) to activate Hedgehog-mediated transcription, by Stats to activate cytokine-mediated transcription, and by Ets proteins to activate MAPK-mediated transcription, as well as by many other transcription factors [58–63] (Figure 1C). At least some of these interactions seem to be direct, suggesting that CBP has integrated multiple adaptor domains into a single molecule. Several other HAT complexes, including STAGA, TFTC, and Tip60, are recruited to transcriptional activators through the TRRAP subunit, a very large protein containing multiple sites for protein–protein interactions [64]. Such a mechanism may promote cooperative recruitment of HAT activity by different transcription factors bound to the same enhancer region.

Interestingly, CBP acetylates not only histone substrates, but many transcription factors as well. Such acetylation can either enhance or inhibit their transcriptional activity by altering nuclear localization, protein stability, DNA binding, or interaction with coactivators [65]. For instance, CBP/p300 is recruited to the promoters of Wnt target genes by interactions with β-catenin and the DNA-binding protein TCF. In addition to acetylating histones, it acetylates β-catenin, reducing its ability to activate *myc* expression and its affinity for TCF, and TCF, reducing its affinity for β-catenin [66,67•,68,69]. Conversely, intercellular signaling can lead to post-translational modifications of CBP itself, regulating its activity [11] and thus indirectly influencing other signaling pathways. An example is phosphorylation of CBP by IKKα, which promotes CBP binding to the transcription factor NF-κB rather than to p53, leading to tumor cell proliferation rather than apoptosis [70•]. These bidirectional interactions between CBP and signaling pathways allow it to integrate multiple inputs and translate them into changes in gene expression.

Conclusions

A diverse set of mechanisms allows signal-regulated transcription factors to recruit the general transcriptional machinery and alter target gene expression. Complexes that alter chromatin structure or recruit RNA polymerase may interact with transcription factors through large multifunctional subunits or individual specialized subunits. In many cells, different forms of the same complex can be recruited to different promoters, and may also have distinct functional properties. Subunits of regulatory complexes can themselves be the targets of regulation by signaling pathways. A special case of this is the replacement of entire transcriptional regulatory complexes in specific developing tissues, but complexes can also be altered by post-translational modifications or conformational changes induced by transcription factor binding. Such effects provide a mechanism through which signaling pathways can influence each other in the nucleus by indirectly altering the potential to regulate target gene expression.

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