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GENETICS

Chromatin remodelling and the transcription cycle

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Transcription by RNA polymerase II (Pol II) occurs in the context of chromatin within a eukaryotic cell. Chromatin is generally inhibitory to transcription, so a variety of mechanisms are required to activate transcription from a nucleosomal template. One of the first steps is that large co-activator complexes interact with small activator proteins to identify gene promoters that are ready to be transcribed. Nucleosome remodelling complexes that use energy from ATP to move or displace nucleosomes from DNA facilitate the recruitment and assembly of these complexes on the promoter and enable rapid gene activation. Even during transcription elongation, nucleosomes must be removed for efficient passage of the polymerase. Furthermore, these same nucleosomes must be reassembled rapidly and modified appropriately following passage of the polymerase to prevent inappropriate initiation of transcription from promoter-like elements within the coding region.

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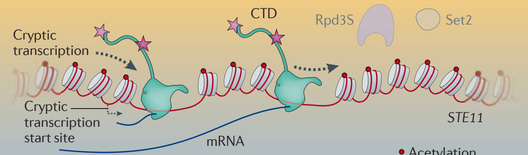
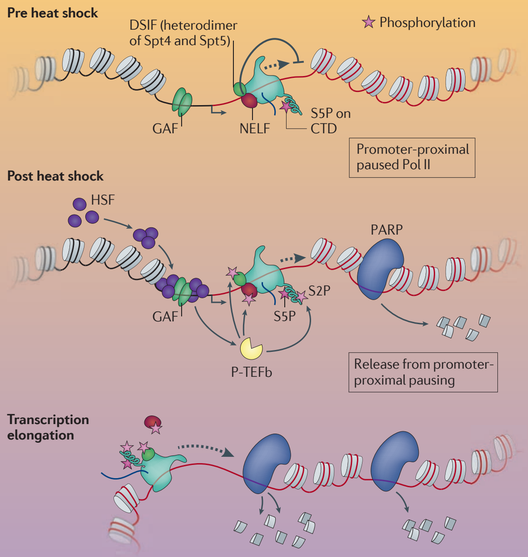
Example of chromatin regulation during elongation: *STE11* in yeast

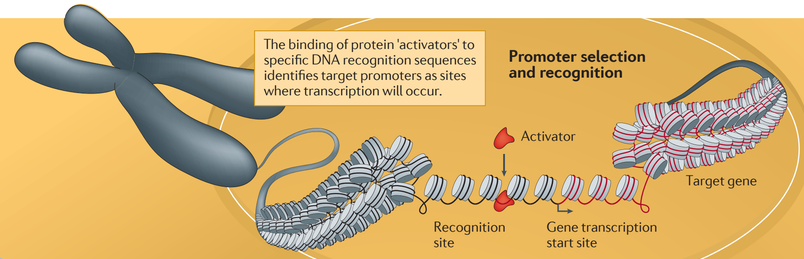


In yeast, loss of the histone deacetylase complex Rpd3S, or the H3K36 methyltransferase Set2 results in hyperacetylation of the coding region of genes such as *STE11*. Promoter-like regions within the coding region are then able to recruit Pol II and components of the general transcription machinery, and transcription can be initiated inappropriately at these cryptic initiation sites. Thus, proper regulation of histone assembly, disassembly and modifications are critical to control transcription on a chromatin template.

Example of regulation by polymerase pausing: heat shock genes in *Drosophila melanogaster*



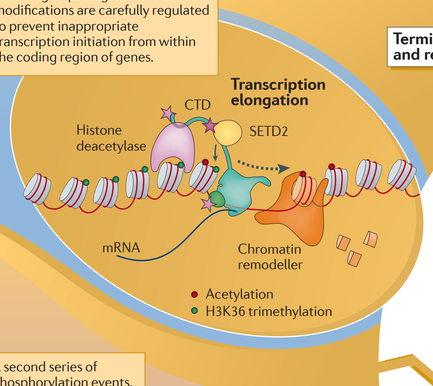
Heat shock genes in *Drosophila melanogaster* are rate-limited during early elongation. Prior to heat shock, GAF, co-activators and the GTFs are bound at *Hsp70* and Pol II is present at the promoter-proximal pause site, where it sits in a poised state ready to resume productive elongation. Heat shock induces trimerization of the transcription factor HSF, which then binds to the promoter of *Hsp70*. Binding of HSF is required, but is not sufficient, to recruit the activating kinase P-TEFb, which phosphorylates the inhibitory factors NELF and DSIF, as well as serine 2 of the CTD, resulting in release of Pol II into productive transcription elongation. PARP catalyses formation of ADP-ribose polymers, and along with HSF and GAF is required for nucleosome loss at *Hsp70* following heat shock. Nucleosome loss preceeds the passage of Pol II and facilitates gene activation.

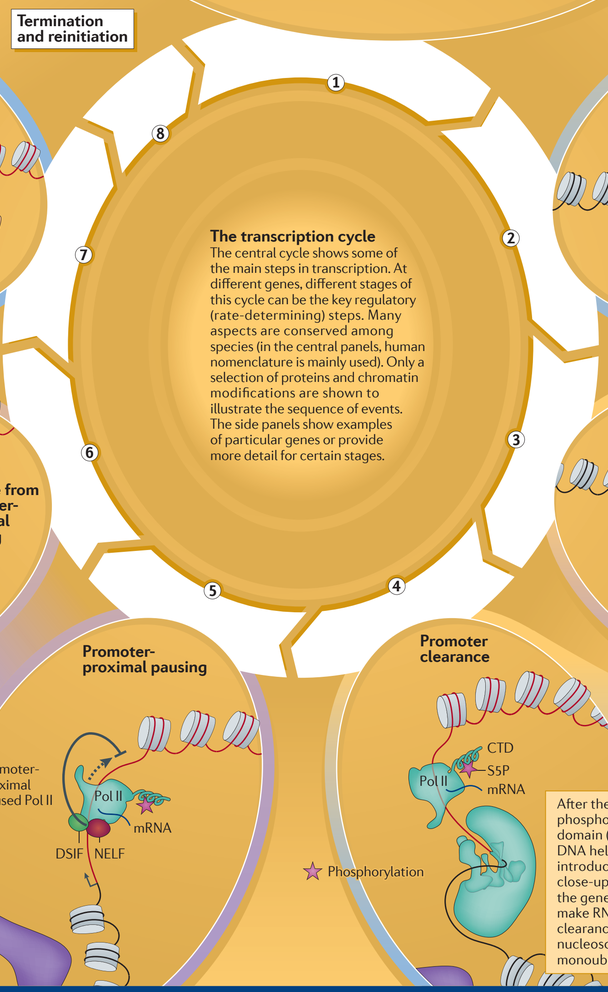


The binding of protein 'activators' to specific DNA recognition sequences identifies target promoters as sites where transcription will occur.

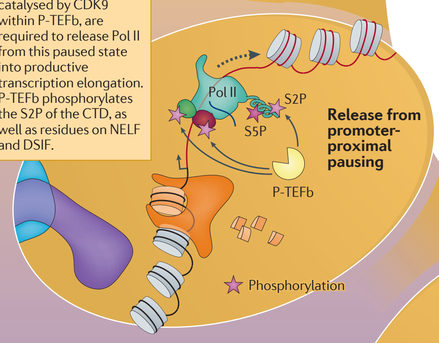
Promoter selection and recognition

During transcription elongation, the phosphorylated residues on the CTD provide binding sites for chromatin modifiers such as SETD2 (Set2 in yeast and flies), which methylates H3K36. Efficient transcription requires chromatin remodelling by complexes such as SWI/SNF and RSC, and histone chaperones such as the FACT complex and SPT6. Nucleosomes must be displaced ahead of Pol II and reassembled following its passage. Histone modifications are carefully regulated to prevent inappropriate transcription initiation from within the coding region of genes.



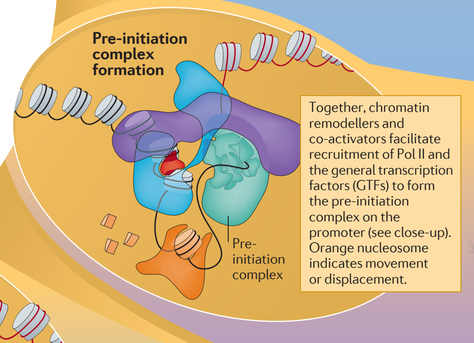


A second series of phosphorylation events, catalysed by CDK9 within P-TEFb, are required to release Pol II from this paused state into productive transcription elongation. P-TEFb phosphorylates the S2P of the CTD, as well as residues on NELF and DSIF.

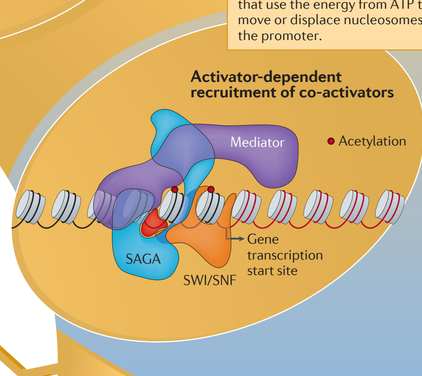


At some genes, after Pol II transcribes a short distance into the gene, it pauses at a region of DNA known as the promoter-proximal pause site. Pol II is prevented from moving forward from this region by inhibitory factors such as NELF and DSIF. (Note: NELF is not present in yeast.)

After the pre-initiation complex has formed, CDK7 within TFIIH phosphorylates the serine-5 position (S5P) within the carboxy-terminal domain (CTD) of the largest subunit of Pol II. Around the same time, the DNA helicase XPB unwinds 11–15 bases of DNA at the promoter to introduce a single-stranded template into the active site of Pol II (see close-up above). Transcription begins as Pol II dissociates from many of the general transcription factors, clears the promoter and begins to make RNA. During pre-initiation complex formation and promoter clearance, several different histone modifications are deposited on nucleosomes at the promoter, including H3K4 trimethylation and H2B monoubiquitylation (see side panel).

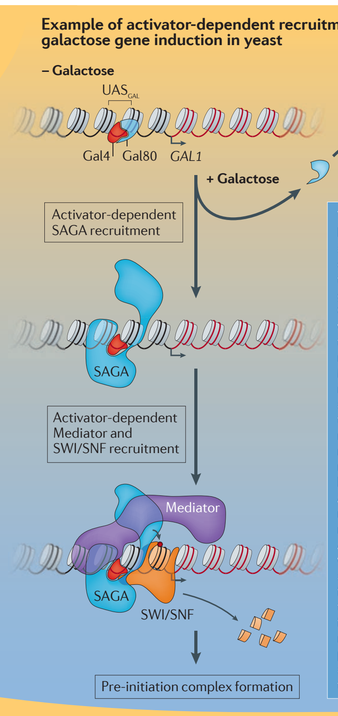


Together, chromatin remodellers and co-activators facilitate recruitment of Pol II and the general transcription factors (GTFs) to form the pre-initiation complex on the promoter (see close-up). Orange nucleosome indicates movement or displacement.



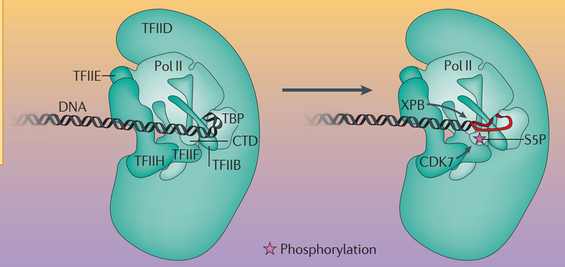
Activators recruit large multi-subunit co-activators such as Mediator, the histone acetyltransferase complex SAGA, and chromatin remodelling complexes (such as SWI/SNF) that use the energy from ATP to move or displace nucleosomes at the promoter.

Example of activator-dependent recruitment: galactose gene induction in yeast

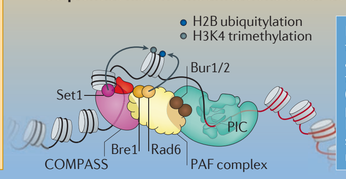


The Gal genes in yeast have been extensively studied and are illustrative of the role of activators in initiating transcription. The presence of galactose releases the activator Gal4 from its repressor Gal80, which becomes sequestered in the cytoplasm by Gal3. Gal4 recruits SAGA, followed by Mediator and the chromatin remodeller SWI/SNF. Histone acetylation by SAGA stimulates the remodelling of promoter nucleosomes by SWI/SNF (orange nucleosome indicates movement); remodelling enhances the kinetics of activation at *GAL1*. At other genes, chromatin remodelling may be a requirement for activation. At *GAL1*, SAGA and Mediator work together to recruit Pol II and the general transcription factors to the promoter, where the pre-initiation complex forms. In this example, recruitment of Pol II and pre-initiation complex formation are the rate-limiting steps during transcription activation.

The pre-initiation complex prior to promoter clearance



Sequential histone modifications occur at promoters



Histone H3 lysine 4 (H3K4) trimethylation is associated with active transcription. In yeast, this mark is deposited by Set1 (within COMPASS) and requires prior ubiquitylation of histone H2B by Rad6 and Bre1. For simplicity, these proteins are not shown in other panels.

References

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Abbreviations

CDK, cell division protein kinase; COMPASS, complex proteins associated with Set1; DSIF, DRB sensitivity-inducing factor; GAF, GAGA factor; HSF, heat shock factor; *Hsp70*, heat shock protein 70; NELF, negative elongation factor; PARP, poly(ADP)-ribose polymerase; P-TEFb, positive transcription elongation factor b; SWI/SNF, switch/sucrose non-fermentable; TBP, TATA box binding protein; TFII, transcription factor II; Tra1, transcription associated protein 1; UAS, upstream activating sequence

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