Commentary

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Nucleosomal Barrier to Transcription Structural Determinants and Changes in Chromatin Structure Cancer

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Commentary

The packaging of DNA into chromatin has an impact on all DNA activities. Nucleosomes act as a substantial impediment to transcription, posing crucial concerns about the nature of the impediment and how it might be overcome. DNA sequencing, DNA–histone interactions, and RNA polymerase II (Pol II) backtracking have all been shown to contribute to the establishment of the barrier. After Pol II partially uncoils it from the histone octamer and backtracks the enzyme, nucleosomal DNA recoils on the octamer, keeping Pol II in the arrested state. Transcription factors include histone chaperones and transcription factors. To aid transcription via chromatin, TFIIS, TFIIF, and FACT all use separate molecular mechanisms.

Extensive chromatin remodelling is induced by RNA polymerase II (Pol II) transcription, which is aided by histone chaperones and elongation factors and is accompanied by restricted histone exchange. At the same time, histones are only fully evicted from highly transcribed genes, hence Pol II normally encounters nucleosomes every 200 bp DNA area during transcription. The presence of nucleosomes on transcribed genes creates two types of barriers to Pol II transcription. Each nucleosome in yeast and *Drosophila* has a barrier where Pol II is halted after transcribing 15 and 50 bp from the nucleosome boundary; similar barriers are also seen *in vitro*.

When the active site of the enzyme is located 10 bp upstream of the first (+1) transcribed nucleosome in *Drosophila*, a substantially higher barrier of the second kind is produced. The relative involvement of the +1 nucleosome and negative elongation factors to this halt, particularly for highly expressed genes, is not apparent. When Pol II hits a roadblock during transcript elongation, such as DNA-bound proteins or DNA sequences that prevent the next NTP from being added, the polymerase backtracks by sliding the transcription bubble and RNA-DNA hybrid upstream along the template. This causes transcriptional inhibition by displacing the RNA 3' end from the Pol II active site.

TFIIS, a protein factor that works in tandem with the Pol II active centre to induce cleavage of the transcript, is required for rapid alleviation of arrest. The downstream RNA segment is released after the 3' end is aligned with the active centre. Although arrest sites are uncommon in DNA, backtracking and arrest are common features of Pol II complexes halted right downstream (+17 to +32) of transcription initiation. This could be critical for freshly formed Pol II complexes' interaction with the +1 nucleosome. *In vitro*, a single nucleosome typically produces a high, asymmetrical first-type barrier for Pol II transcription. However, the *in vivo* identified putative regulatory -10 barrier of the second type has not been replicated *in vitro*. The strong nucleosomal barriers of +15 and +50 are nucleosome-specific, Pol II-specific, and have been described for all organisms studied, from yeast to humans

The barrier arises at distinct positions within the + (10-20) and +(40-50) regions on every given DNA sequence wrapped onto a nucleosome. Thus, both *in vitro* and *in vivo*, these nucleosomal barriers are “universal signatures” of transcription through chromatin by Pol II. The development of the barrier is aided by DNA-histone interactions as well as Pol II pausing and backtracking.

Intranucleosomal DNA-histone interactions in single nucleosomes were mapped, and two regions of strong interactions [+(25-35) and +(70-80)] were discovered to have a significant impact on the rate and efficiency of Pol II progression through a nucleosome, contributing to the formation of the +15 and +50 nucleosomes.

A second DNA region, +(89-102), known as the polar barrier sequence, regulates the overall affinity of DNA-histone interactions in a sequence-specific manner, contributes to +50 pausing, and defines the overall height of the nucleosomal barrier to transcription. A single snip in nucleosomal DNA can

also have a significant impact on the height of the barrier. After Pol II moves beyond position +49, the nucleosomal barrier is considerably removed. On the surface of the histone octamer at position +49, a tiny intranucleosomal DNA loop (-loop) containing Pol II develops. The -loop is sustained by Pol II-histone contacts, which substitute DNA-histone interactions transiently and locally; the high efficiency of -loop generation is characteristic of the Pol II-specific method of transcription through chromatin.

During this process, the formation of the -loop causes uncoiling of the 100-bp DNA area in front of the enzyme, allowing for continued transcription through the nucleosome and efficient survival of nearly all histones (with the exception of one H2A/H2B dimer that is displaced by Pol II). Allosterically maintained intranucleosomal histone-histone interactions contribute to the high efficiency of histone survival during transcription. According to a recent structural analysis, after Pol II reaches the strong +50 barrier, the enzyme backtracks and nucleosomal DNA re-coils on the octamer, thereby arresting Pol II.