Genome Biology

RESEARCH HIGHLIGHT

Evolutionary insights into genome-wide nucleosome positioning

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Abstract

A new study takes an evolutionary approach to investigate to what extent nucleosome positioning is determined by underlying sequence or by *trans*-acting factors.

Keywords Evolution, genome-wide organization, nucleosome positioning, poly(dA:dT) sequences, yeast.

The development of genomic technologies has enabled the application to whole genomes of approaches previously used to map nucleosome positions over specific genes A resulting observation was that, whereas the positioning of nucleosomes over single genes appeared noisy, when many genes are aligned by their transcriptional start sites a striking organization emerges.

The discovery of a genome-wide organizational pattern, which consists of a nucleosome-depleted region just upstream of the transcriptional start site, followed by an array of ordered nucleosomes extending over the coding region (Figure 1), has generated considerable interest into what underlies this organization. It has been known for some time that the structural properties of DNA can influence where nucleosomes are assembled, so the idea that the sequences of genomes could have evolved to direct the positioning of nucleosomes is feasible. However, a counterpoint to this is that it has also been known for some time that nucleosome positioning is to some extent dynamic and can, for example, change within different tissues of the same organism. In addition, it is known that there are cellular factors capable of repositioning nucleosomes. This, together with the observation that chromatin assembled *in vitro* does not fully recapitulate that found in cells, has led to a vigorous debate as to the relative contributions of *trans*-acting factors and DNA-directed signals in the positioning of nucleosomes.

Hughes *et al.* [1] adopt an elegant approach to investigate this phenomenon, relying on the evolutionary diversity of the *Hemiascomycota* yeast. The foundation for this was laid by previous studies that identified considerable diversity in nucleosome spacing, together with other aspects of chromatin organization, in different species of yeast [2]. This prompted Hughes *et al.* to characterize the chromatin assembled on DNA from one species when propagated as an artificial chromosome in another species. In general, chromatin adopts an organization related to the host organism rather than to the species from which the DNA originated. This indicates that, over the majority of the genome, *trans*-acting factors play a dominant role in establishing nucleosome positioning; consistent with previous studies showing that factors present within yeast extracts are capable of converting *in vitro* assembled chromatin to a conformation similar to native chromatin [3]. Over coding regions there is evidence that the enzymes Chd1 and Isw1 function with partial redundancy to fulfill this role [4]. Both of these proteins have the ability to reposition nucleosomes along DNA in an ATP-dependent reaction that results in a more uniform spacing between adjacent nucleosomes.

Hughes *et al.* did, however, find some evidence to suggest a role for DNA sequences in nucleosome organization [1]. Nucleosome-depleted regions (NDRs) at promoters were to some extent conserved relative to their endogenous positions, with a subset showing greater conservation. This subset shows an enrichment for poly(dA:dT) sequences, suggesting that for some NDRs these sequences play an important role in chromatin organization. How poly(dA:dT) sequences act to deplete nucleosomes is less clear. Previous studies have highlighted the correlation between the presence of poly(dA:dT) tracts and reduced chromatin assembly [5]. However, Hughes *et al.* point out that *in vitro* assembly does not fully recapitulate the depletion of nucleosomes observed over poly(dA:dT) tracts observed *in vivo*. This suggests that there may be a role for *trans*-acting factors even at poly(dA:dT)-containing NDRs. Candidates include

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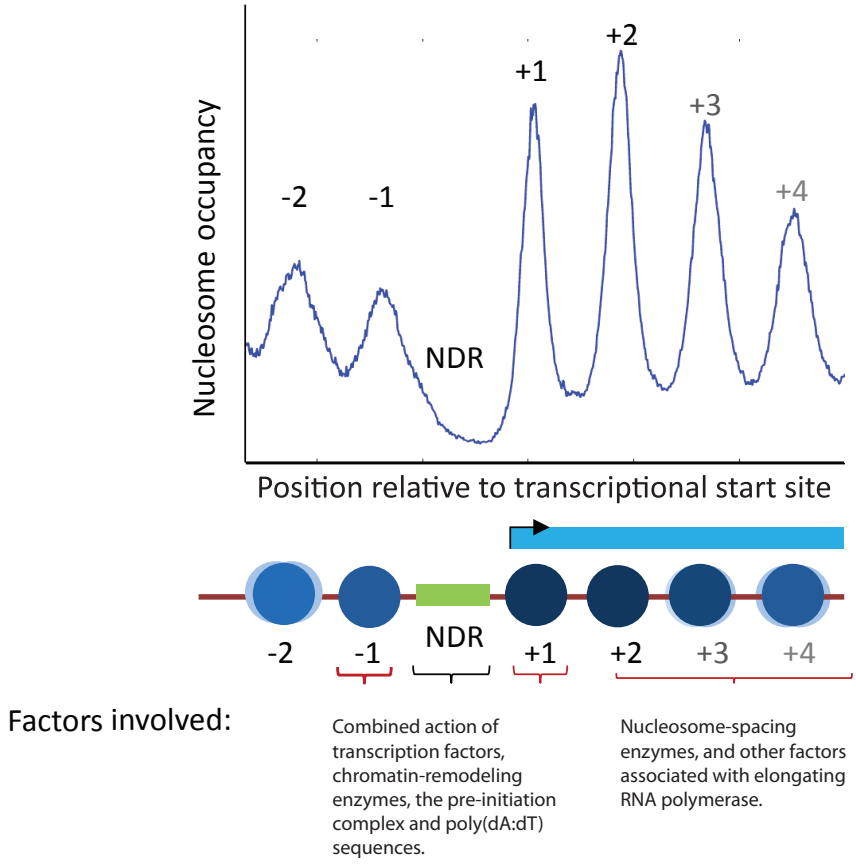

Figure 1. Factors involved in maintenance of genome-wide organization. As a first step, nucleosome-depleted regions (NDRs) are generated either as a result of poly(dA:dT) DNA sequences or by binding of other factors. This is followed by recruitment of chromatin remodelers and pre-initiation complexes (at promoters), which may fine-tune positioning of +1/-1 nucleosomes. Nucleosome-spacing enzymes such as Chd1 and Isw1 that are linked to the elongation phase are responsible for the positioning of downstream nucleosomes (+2 onwards).

abundant sequence-specific transcription factors such as Reb1, and remodeling enzymes that may act to remove nucleosomes such as the RSC complex [6,7]. Another intriguing possibility is that the structural features of poly(dA:dT) repeats may favor non-specific interactions with many transcription factors, and that this in turn could act to reduce nucleosome occupancy [8].

The organization of nucleosomes over coding regions appears strongest at the 5' ends of genes, with the strength of positioning decaying farther into coding regions. Furthermore, enzymes such as Chd1 that are responsible for spacing are intimately associated with transcriptional elongation [9]. These observations suggest that the process of nucleosome spacing is in some way coupled to transcription. However, it has recently been observed that nucleosome spacing can to some extent be established in an extract that does not support transcription [3]. In addition, nucleosome positioning over coding regions is substantially retained following inactivation of RNA polymerase [10]. As a result the nature of the coupling between the nucleosome-spacing reaction and transcription is unclear.

The approach taken by Hughes *et al.* makes an unanticipated contribution to this debate, as they found that changes in transcription occur when DNA sequences are transferred from endogenous to exogenous contexts [1]. A dramatic example of this is provided by the occurrence of NDRs within coding regions in the heterologous context [1]. Formation of the NDR is not directed by the nucleosome-excluding properties of the heterologous DNA, as in such a case NDRs would also be observed in the donor cell. These ectopic NDRs are associated with intragenic transcripts and, remarkably, they are flanked with reasonably well-organized nucleosomes. This observation, together with shifts in the positioning of the +1 nucleosomes at genes with altered transcription in the heterologous context, supports the coupling of the nucleosome-spacing reaction to transcription. The extent to which nucleosome positioning influences the transcription start site, or to which transcription directs the

phasing of nucleosome arrays, is yet to be determined. However, it is quite possible that additional insights will be provided by this ancient clade of microorganisms.

Abbreviations
NDRs, nucleosome-depleted regions.

Competing interests
The authors declare that they have no competing interests.

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