Rotational positioning of regulatory elements within nucleosomes

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1 Regulation of gene expression depends on the rotational positioning

One of the key factors in the regulation of gene expression is binding of transcription factors to their response elements. This binding is well known to depend on rotational orientation of the binding sites in the nucleosome [6, 7, 12, 9, 1].

Typically, the binding occurs if the binding site is exposed. The transcription factor binds to the DNA with the highest affinity when the recognition sites are oriented away from the histone octamer. For example p53 binds preferentially to the nucleosomes when the minor grooves of the recognition sequences are oriented outwards [9]. Another example is glucocorticoid receptor which favors the binding sites positioned in the major grooves facing out [6]. In both cases the transcription factor binding decreases when rotational positioning of the recognition sites is changed, being abolished when the sites face the histone octamer [6, 9].

2 Computational mapping of the nucleosomes

The rotational setting can be determined by any of few available techniques, which allow a single-base resolution mapping of the nucleosomes on DNA

[3, 11, 2]. We used the DNA bendability matrix derived by [3] to study the rotational positioning of TATA boxes and splice junctions.

This technique had been tested on the set of nucleosome DNA sequences experimentally mapped with high accuracy, including the crystallized nucleosome data. The test demonstrated ± 1 base fit [3] to the experimental positions.

3 Rotational positioning of the TATA boxes

For the analysis of the TATA boxes we extracted[5] DNA sequences from the Eukaryotic Promoter Database [8] and mapped nucleosomes on these sequenced synchronized around the TATA box.

Our results show that the nucleosome DNA sequence harboring the TATA box encodes alternative rotational positions for the same piece of DNA. This may serve for switching the gene activity on and off.

4 Rotational positioning of the splice junctions

When we applied[4] this approach to DNA sequences containing splice junctions from five different species[10], we found the junctions to be preferentially located within nucleosomes. Moreover, the orientation of guanine residues at the GT- and AG-ends of introns within the nucleosomes are such that the guanines are positioned nearest to the surface of histone octamers, 3 and 4 bases upstream from the local DNA pseudo-dyads passing through minor grooves oriented outwards. Since the guanine residues are the most vulnerable to spontaneous damage within the cell (primarily, depurination and oxidation) such positioning of the splice junctions minimizes the damage that is caused by free radicals and highly reactive metabolites.

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