DNA NUCLEOSOME ORGANIZATION OF THE FUNCTIONAL GENES REGIONS AND ITS RELATION TO GENE EXPRESSION LEVEL

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Keywords: gene expression pattern; nucleosome positioning

Summary

Motivation: DNA nucleosome organization is an important factor in gene expression patterning. The nature of the context signals determining nucleosome formation sites are not completely understood. Given these considerations, the relation between nucleosome positioning and gene expression regulation appears of great interest.

Results: Taxon-specific nucleosome organization of the yeast and mammalian core promoters was identified. Positive correlations were established between characteristics potentially related to nucleosome positioning of the yeast core promoter and gene expression level. The context parameters of the DNA nucleosome organization differ by the distribution pattern in the mammalian and yeast promoters.


Introduction

DNA packaging in chromatin structure is an important factor in the regulation of the status of gene expression pattern in eukaryotes. The nucleosome positioning in certain circumstances may both activate and repress gene expression. It is now known that nucleosome formation in the genomic DNA is determined by the interaction of different regulatory and structural proteins with their cognate sites and context nucleosome positioning signals. Taken together, the interactions form the code of chromatin nucleosome organization (Lowary, Widom, 1997; Kiyama, Trifonov, 2002).

It may be assumed that nucleosome formation depends on the gene expression level and highly expressed genes have specific features, which increase transcription efficiency by optimization of context characteristics. Our previous observations demonstrated significant correlations between DNA context of the promoter and 5'UTR regions and the expression level (Kochetov et al., 2002; Pichueva et al., 2004). We have also previously shown that the nucleosome formation potential is greater in tissue-specific gene promoters than in the genes expressed in many tissues and housekeeping genes (Levitsky et al., 2001). Hence, the capability of nucleosome positioning in the promoter region may serve as a regulatory factor of the gene expression level. Here, we present the results of a computational analysis of the characteristics potentially related to nucleosome positioning in the core promoters of the yeast and mammalian genes.

Materials and Methods

Saccharomyces cerevisiae mRNAs were extracted from the EMBL nucleotide sequence databank. Full-size 5'UTRs were selected from the entries containing a description of the transcription start sites (TSS) and complete coding regions. Only the mRNAs with full size 5'UTRs (i.e., containing reference to an experimentally mapped TSS) were used. This resulted in a set of 5'UTRs of 240 yeast genes. To avoid bias due to redundant sequence data in statistical analysis, redundant sequences (CDS homology higher than 70 %) were removed. Finally, the set comprised 5'UTRs of 98 yeast genes with a single TSS and a complete coding sequence. A sample of promoter sequences spanning 150 nucleotides upstream of the major TSS was also compiled and was
combined with the corresponding 5'UTRs; 271 promoter sequences of length 1500 bp ([–1000; +500] with respect to the TSS) of the eukaryotic genes (mostly mammalian) were selected from the TRRD database. All the promoter sequences were aligned with the TSS.

The Codon adaptation index (CAI) (Sharp, Li, 1987) was calculated by the CodonW 1.3 program (http://www.molbiol.ox.ac.uk/cu) and was used as a measure of the yeast gene expression level. The PHASE and RECON computer programs were used in comparative analysis of the nucleosome formation ability. The RECON program calculates the nucleosome formation potential (NFP) (Levitsky et al., 2001). The PHASE program estimates the density of dinucleotides phased with helical turn periodicity in DNA sequences. The PHASE program yields the function PDD (periodic dinucleotide density) (Levitsky et al., this issue). In the current study, we applied PDD only to AA and TT dinucleotides, smoothing window size was 145 bp.

**Results**

The profiles of the PDD and NFP for the promoter and 5'UTR regions of the yeast genes sequences aligned with the TSS is shown in Fig. 1. Clearly, the PDD is maximal in the wide [-100; +50] region overlapping the TSS. The NFP has, as a rule, constant values in the upstream region and slightly increased in the downstream.

The correlations between the PDD values and CAI and also between NFP values and CAI were determined (Fig. 2A, B). The correlation coefficients are mostly positive. Significance (p < 0.05) is observed in the [+5; +30] region for NFP, and the highest positive correlations in the [-90; -70] and [-20; +20] regions for PDD.

Unlike yeast, the core promoters and downstream regions of *Mammalia* show other PDD and NFP profiles (Fig. 3): both profiles start to decrease about 400 bp upstream of the TSS and remain low within the downstream region.

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Fig. 1. Profile of periodic dinucleotide density (PDD) of AA and TT dinucleotides and nucleosome formation potential (NFP) for the promoter and 5'UTR regions of yeast genes.

Fig. 2. Profile of the correlation coefficients between: (A) the periodic dinucleotide density (PDD) and CAI, (B) the nucleosome formation potential (NFP) and CAI for the promoter and downstream regions of the yeast genes.

Unlike yeast, the core promoters and downstream regions of *Mammalia* show other PDD and NFP profiles (Fig. 3): both profiles start to decrease about 400 bp upstream of the TSS and remain low within the downstream region.
Discussion

It is known that dinucleotides AA and TT periodicities are most important in nucleosome site formation. Particular periodicities of these dinucleotides are related to the DNA curvature, thereby facilitating nucleosome formation (Ioshikhes et al., 1996). The positive significant correlation between CAI and PDD for AA and TT dinucleotides found for the promoters may be related to DNA conformation just upstream of the TSS. This DNA conformation is very important in transcription initiation. The profiles of the correlation coefficients (Fig. 2A, B) along the yeast promoters and 5'-UTR regions revealed a wide range of positive correlations (from –100 to +40 bp). This may be interpreted as a tendency of the core promoters of the yeast highly expressed genes to form nucleosomes with a higher probability. It should be noted that the context parameters of the DNA nucleosome organization differ by the distribution pattern in the mammalian and yeast promoters.

Acknowledgements

The work was supported by the RFBR (grants Nos. 02-04-48802, 03-04-48555, 03-04-48829, 01-07-90376, 02-07-90355, 03-07-96833, 03-07-90181, 03-07-06078); Ministry of Industry, Science, and Technologies of the Russian Federation (grant No. 43.073.1.1.1501); Russian Federal Research Development Program Research and Development in Priority Directions of Science and Technology (contract No. 38/2004); SB RAS (integration project No. 119); NATO (grants Nos. LST.CLG.979816), Project No. 10.4 of the RAS Presidium Program “Molecular and Cellular Biology”.

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