3D organization of chromosomes mediated by RNAPII complex contacts in human genome

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The 3D organization of a eukaryotic genome plays an important role in nuclear gene expression. It is a challenging problem to analyze higher-order chromosomal organization affecting transcription regulation in human. Transcription in nucleus is concentrated within large discrete foci, assuming that genes are organized into "transcription factories" containing RNA polymerase II and other protein complexes. Until recently, studies of this organization were limited by light microscopy and electron microscopy methods. The development of chromosome conformation capture (3C) methods allowed studying genome-wide chromosomal contacts by using only molecular methods. Chromosome Conformation Capture (3C) and similar microchip techniques along with traditional in situ techniques have demonstrated that chromatin interactions exist and regulate transcriptional and epigenetic states of genes. Several papers recently suggested high-throughput sequencing technique for detection of chromosome loops and interactions in whole-genome scale, such as Hi-C, ChIA-PET [1,2]. Nowadays, numerous 3C-based methods have been developed to reconstruct the 3D organization of eukaryotic genomes including model organisms [4]. We are working on development and integration of computer methods of genome structure and transcription factor binding sites analysis in embryonic stem cells [5].

Genome-wide Chromatin Interaction Analysis with Paired-End-Tag sequencing (ChIA-PET) technology has presented long-range chromatin interactions associated with specific protein factors. ChIA-PET experiment with RNA polymerase II (RNAPII) shows that widespread promoter-centered interactions further could be classified as intra-genic, extra-genic and

inter-genic interactions [1]. Such interactions could be further aggregated into higher-order clusters, there proximal and distant genes are engaged through promoter-promoter interactions. Computer analysis of gene location and chromosome interacting sites revealed strong genome-wide association to transcription factor binding sites. Thus, analysis of chromatin interactions mediated by estrogen binding (ER-mediated interactome) confirmed associations of ER binding sites to RNAPII [3]. Overall, most genes with promoter-promoter interactions are highly active and could transcribe cooperatively, and that some interacting promoters could influence each other, implying combinatorial complexity of transcriptional controls. Comparative analyses of different cell lines (such as MCF-7, K562) imply that cell-line specific chromatin interactions could provide structural framework for the transcription. We found enrichment of ChIP-seq defined transcription factor binding sites from ENCODE project in human genome in spatial proximity to chromatin bound contacting sites. This work gives new insights to study the gene transcription and regulation from the spatial perspective in a whole-genome scale.

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