Abstract

There is increasing evidence that the cell nucleus is highly organized. A growing number of defined bodies and substructures with different functions has already been identified. Non random radial positioning of chromosome territories and single genes was observed. Moreover, close spatial association upon activation was reported for some selected functionally related genes. However, little is known about the mechanisms or factors that determine the nuclear positioning and it is unclear whether the spatial association of active genes is a general aspect for co-expression or if it applies only to special examples.

This study was designed to provide an unbiased and general insight into the linear and spatial organization of active genes. Expression profiles derived from a microarray study on human adipocyte differentiation were analyzed to assess the chromosomal arrangement of co-transcribed genes. The different analyses revealed a frequent grouping into tandems suggesting a non random linear organization of the human genome. Seven genes were then selected based on their similar expression profile and were simultaneously visualized by 3D combinatorial multiplex fluorescence in situ hybridization (M-FISH). The radial organization of these seven genes was found to be primarily determined by local gene density and did not correlate with their transcription levels. Furthermore, it could be shown that close spatial association of active genes is not restricted to some special examples but can also be observed for co-expressed genes of unrelated function. In addition, it could be demonstrated that the global spatial organization of active genes is non random and is preserved between different nuclei under different physiological conditions. This work provides further insight into the linear- and nuclear architecture of the human genome. It is a step towards a better understanding of complex organizational patterns involving multiple genes.

Keywords: nucleus, spatial organization, active genes, chromosome, transcription factory, fluorescence microscopy, 3D multiplex FISH, adipogenesis, hMADS