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Review

Moving chromatin within the interphase nucleus-controlled transitions?

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Abstract

The past decade has seen an increasing appreciation for nuclear compartmentalization as an underlying determinant of interphase chromosome nuclear organization. To date, attention has focused primarily on describing differential localization of particular genes or chromosome regions as a function of differentiation, cell cycle position, and/or transcriptional activity. The question of how exactly interphase chromosome compartmentalization is established and in particular how interphase chromosomes might move during changes in nuclear compartmentalization has received less attention. Here we review what is known concerning chromatin mobility in relationship to physiologically regulated changes in nuclear interphase chromosome organization.

Keywords: Interphase chromosome; Chromatin mobility; Nuclear organization

Contents

1. Overview of interphase chromosome organization

Perhaps the most striking element of nuclear organization of interphase chromosomes is their partitioning into distinct "chromosome territories" (CTs) [1–3]. First inferred from the chromosomal distribution of DNA repair sites when a small region of the nucleus was irradiated by UV light [4], CTs are now best visualized by in situ hybridization using chromosome-specific probe sets [5]. Analysis using fluorescence in situ hybridization initially suggested the absence of overlap between CTs or even subchromosomal regions. However, higher resolution analysis has revealed significant, local chromosome intermingling between chromosome territories [6]. While much of this intermingling may be non-specific, new molecular methods such as "3C" (chromosome conformation capture) are beginning to identify examples of specific interactions between distant gene loci separated by a number of Mbp on the same chromosome or even on different chromosomes [7].

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Superimposed on the organization of chromosomes into separate CTs is the non-random location and orientation of individual CTs within interphase nuclei. In a number of species, including Drosophila [8] and yeast [9], chromosomes assume a Rabl conformation, at least in some tissue cell types, with centromeres clustered in a chromocenter at one end of the nucleus and telomeres at the other side. Interestingly, in many Drosophila epithelial cells the chromocenter is located at the apical end of the nucleus. Even in cells without a Rabl conformation, centromeres and telomeres often localize at characteristic locations relative to the nuclear periphery, nucleolus, and nuclear interior depending on the cell type and cell cycle stage [10–12], with centromeres again forming chromocenters in some cell types. Blocks of heterochromatin also frequently localize to the nuclear or nucleolar periphery.

Early replicating chromosome regions tend to be localized more towards the nuclear interior versus late replicating regions [13,14]. Gene rich chromosomes are localized more towards the nuclear interior versus gene poor chromosomes [15]. In mammalian cells at least, a similar polarization is observed for gene rich versus gene poor chromosome regions [14]. In some cell types, these gene rich genomic regions associate closely with SC-35 domains which correlate with interchromatin granule clusters (IGCs) [16]; in other cell types, active genes are found clustered near foci of RNA polymerase II staining, called "transcription factories" [17]. A change in intranuclear positioning associated with transcriptional activation away from the nuclear periphery or chromocenters and towards the nuclear interior also has been described for a number of individual genes [18,19]. This includes examples of movement of specific genes towards IGCs [20] or transcription factories [17,21]. In some cases, particularly for clusters of active genes, a looping out from the main CT occurs [22–25], which may be associated with targeting to specific nuclear bodies. Conversely, a repositioning of genes to the nuclear periphery or chromocenters has been observed after transcriptional repression [26–28]. In contrast, in budding yeast many genes move to the nuclear periphery and become associated with nuclear pores upon gene activation [29].

Whereas most attention to date has focused on documenting these examples of non-random interphase chromosome nuclear positioning, what has not yet been examined carefully is how this highly non-random nuclear organization is established. Do gene loci move in the nucleus through random diffusion or directed movements? Is this organization established largely as nuclei reform after mitosis or do chromosomes move at all times during the cell cycle? In this review we will focus on different types of chromatin movements observed in interphase nuclei, their physiological context, and how they might be regulated.

2. The null hypothesis and local chromatin mobility

Conceptually, one can imagine a range of mechanisms accounting for the establishment of non-random intranuclear positioning of interphase chromosomes. At one extreme is the "null hypothesis" in which non-random interphase chromosome positioning would be established entirely through regulated attachment/detachment of chromosome loci from specific nuclear compartments and/or other loci. Random diffusion would account for chromosome repositioning between different nuclear locations. At the other extreme, interphase chromosomes would move by directed movements from one location within the nucleus to another. These models are not mutually exclusive, and intermediate models can be proposed as well, including for instance randomly directed mobility driven by energy-dependent processes. In the null hypothesis model, chromatin mobility must be sufficiently fast and long-range to account for observed changes in interphase nuclear positioning. Moreover, this random motion should be energy independent and diffusive in nature. For efficient chromosome repositioning, chromosomes must be able to move significantly faster, over the relevant time period for the observed interphase chromosome repositioning, than the net distance change during the chromosome movements in order to allow sampling of different nuclear compartments. Conversely, if random chromosome mobility is slow or constrained relative to the time and distance scale of observed interphase chromosome repositioning, then active mechanisms underlying interphase chromosome movements must be considered.

3. Local chromatin mobility versus chromosome repositioning in *Saccharomyces cerevisiae*

In the budding yeast *S. cerevisiae*, measurements of local chromatin mobility indicate rapid, localized movements which, although constrained spatially, are fast enough to allow interphase chromosomes to explore a large nuclear subvolume over a biologically meaningful time scale. By tagging a locus near centromere III with GFP-lac repressor bound to a lac operator direct repeat, Marshall et al. [30] were able to track chromatin motion during G1 in diploid cells by measuring the distance between two homologous loci. The mean square change in distance (MSD) versus time interval increased linearly over short time intervals before reaching a plateau at time intervals greater than 100–200 s. The dependence of MSD versus time is commonly used to analyze particle motion. A linear increase over time interval is observed for free diffusion, whereas a linear increase followed by a plateau is observed for particle diffusion constrained within a limited volume. The inferred radius of confinement from these observations was ~0.3 μm. A "constrained diffusion" model was proposed in which local diffusion of chromatin results in rapid movements constrained by tethering of adjacent chromosome sites to nuclear substructure. In budding yeast nuclei, clustering of centromeres near the spindle pole body is eliminated by a mutation in a kinetochore protein or by nocodazole treatment [31]. Interestingly, nocodazole treatment significantly increased the observed radius of constraint to ~0.7 μm, suggesting that microtubules mediate tethering of interphase centromeres in yeast.

Later experiments systematically examined variations in chromosome mobility for different chromosomal locations [32]. Measurements of chromosome IV centromere mobility were quite close to the previously published values for chromosome III, and the mobility of a telomere on chromosome VI was even lower. However, two interstitial chromosome locations, one near