New and Notable

Dynamic Organization of Gene Loci and Transcription Compartments in the Cell Nucleus

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The biochemists of the 1950s and 1960s considered the cytoplasm as a membrane-bound bag of enzymes, whereas the nucleus was considered to be so packed with DNA and related proteins that it surely must be relatively static in nature, save local changes in DNA structure to allow transcription. Today we know that the highly dynamic cytoplasmic actin and microtubule cytoskeletal arrays, with their dozens of associated motors and other accessory proteins, provide the cell with a defined city plan. This plan is a highly organized one, albeit constantly changing with cues from a wide variety of regulatory signals. But what do we know about the structure of the nucleus? In particular, how dynamic is the chromatin as it becomes transcriptionally active? Sinha and colleagues at the National Center for Biological Sciences in Bangalore have now visualized in real time active transcription compartments (TCs) with the use of innovative approaches (1). They show that these TCs are even more dynamic than previously thought.

If we could miniaturize ourselves, enter a cell, and take a ride from the cytoplasm through a nuclear pore and find ourselves navigating within the unbelievably dense array of protein and DNA that resides in the intranuclear space, what would we see? Besides transcription and replication factories, we would encounter a wide variety of nuclear bodies, including nuclear speckles or interchromatin granule clusters, paraspeckles, Cajal bodies, promyelocytic leukemia (PML) bodies, and the perinucleolar compartment, all interspersed between chromosome territories (2,3). We are still at an early stage of understanding what many of these represent. Transcription factories (TFs), each containing perhaps about 30 active RNA polymerase molecules (4), are clearly one of the important nuclear compartments that need to be thoroughly understood.

Because a single TF is capable of transcribing more than one gene, the TFs can be viewed as part of active chromatin hubs (ACHs). Thus, an ACH represents the spatial organization of coregulated genes that allows these genes to loop out of their respective chromatin territory and reach a TF (5). The formation of an ACH requires the sharing of a common transcription apparatus, as well as regulatory sequences leading to an economic way of regulating genes of the hub (6). The formation of ACHs was further supported by the observation of movement of a gene locus that was correlated with its transcriptional activity. The locus was shown to move during transition from a repressed to an activated state with the use of DNA fluorescent in situ hybridization and fixed cells (7). In living cells, such loci were marked with fluorescently tagged DNA binding proteins, which bind to the specific sequences present upstream or downstream of the gene of interest (8). With these methods, a given gene locus was shown to move in different nuclear regions based on the transcriptional activity of the locus, where a similar position of two different loci can lead to different functional implications for different loci (9,10). The observation of TFs by immunostaining in fixed cells and gene loci movement evoked an idea in the field that TFs are fixed and attached to the underlying matrix and that genes are mobile and reach these TFs to form ACHs when they are transcriptionally active.

The article by Sinha et al. (1) in this issue shows that TFs are in fact not fixed. They show for the first time the possibility of visualizing TFs as fluorescently tagged UTP-enriched TCs. The authors show that fluorescently labeled UTP compartments are specific and colocalize with active RNA polymerase. The UTP uptake by these compartments depends on transcription, suggesting the transcriptional relevance of TCs in the nucleus. They use live-cell time-lapse imaging to observe that some of these TCs are highly dynamic within the cell nucleus, surprisingly moving large distances by directional movements that cannot be fully explained by random diffusion. About 70% of the TCs are subdiffusive and may be engaged in transcription as part of ACHs. On the other hand, ~30% of the TCs show ATP- and temperature-dependent diffusions, often directional and over large distances. These mobile TCs may be on their way toward specific locations in the nucleus that can facilitate the formation of ACHs. Consistent with this idea, Sinha et al. (1) observe that the same TC can show a transition from a rapid diffusive movement to a subdiffusive movement, and vice versa.

In general, live cell imaging, with its increasing number of technological advancements, is proving to reveal highly dynamic, directed movements in both the cytoplasm and within the nucleus. How are these intranuclear movements directed? Nuclear myosin I and actin have been implicated in the large-scale movement of gene loci to reach splicing machinery (11), which is concentrated as speckles in the nucleus. For the most part, however, the nuclear counterpart of our understanding of the cytoplasmic cytoskeletal system, together with its well-known and characterized actin-based and microtubule-based molecular motors, remains to be elucidated by future research.

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