Editorial

Where do we go in the nucleus?

The nucleus contains the genetic patrimony of the cell, protects it against environmental stress, and ensures its repair, and its duplication and transcription. The nucleus is limited by a well-defined nuclear envelope. In contrast to cytoplasmic compartments, membranes do not limit nuclear compartments. However, after four decades of extensive investigations, many nuclear domains have been morphologically defined and some have been functionally characterized. The best example is the nucleolus, which is responsible for rRNA synthesis and the assembly of ribosomal subunits. The relationships between the structure of the nucleolus and its functions have been relatively well established. As to nucleoplasmic compartments, many have been morphologically characterized, but their functions are often only partially understood or are still elusive. This includes a variety of nuclear bodies, which are often characterized by the presence of specific proteins, but their role in nuclear functions still remains to be revealed.

The most intensively studied nuclear component is chromatin. The complete DNA sequence of an increasing number of organisms is known, defining the genetic level of genome function. At the chromatin level, we begin to understand the pattern of histone modifications, DNA methylation and chromatin remodelling, together determining the epigenetic level of gene expression. Nuclear architecture is tightly related to chromatin function. Chromatin is present in different structural and functional states. The quantitatively most important state is condensed chromatin, defining chromatin domains in the nucleus. Electron microscopy allows one to observe dispersed chromatin fibers at the periphery of such chromatin domains. An interphase chromosome territory consists of an ensemble of chromatin domains. This large-scale chromatin organization is directly related to genomic activity. The border regions of condensed chromatin, named the perichromatin region, are the sites of both transcription and replication. No such activity can be detected inside condensed chromatin domains.

Nascent transcripts can be visualized as perichromatin fibrils. Transcription factors and RNA processing machineries are found in the same perichromatin compartment. In addition, RNA processing factors are also concentrated in special nucleoplasmic compartments, such as clusters of interchromatin granules (speckles). This domain is probably a site of factor storage or assembly of splicing complexes, as suggested by elegant in vivo experiments (Misteli et al., 1997), but is not a site of transcription. RNA processing factors can be recruited from these domains to sites of transcription. Another nuclear domain in which processing factors accumulate is the Cajal (coiled) body, which has been shown to move rapidly inside the nucleus. The Cajal (coiled) body is found in close proximity of the U2 snRNA locus, suggesting it has some role in snRNA metabolism (Frey and Matera, 2001).

Many studies support the idea that macromolecules, such as protein factors, freely diffuse inside the nucleus. Also, chromatin shows a constrained type of free diffusion, transcriptionally active chromatin more so than transcriptionally silent chromatin. Chromatin movement is relatively local, since it has been shown that complete chromosomes do not move. In contrast, nucleoli have been reported to travel throughout the nucleoplasm (Fung and De Boni, 1988). Evidently, the cell nucleus is highly dynamic at different levels of organization. The molecular details await further analysis of the basics of the molecular organization of the nucleus. In line with this, RNP complex migration would take place by free diffusion from the site of RNA synthesis to the nuclear pores.

To understand basic processes, such as orchestrating the expression of large numbers of genes, replication of the genome and DNA repair, we need to understand the dynamic spatial organization of the nucleus at the molecular level. A major enigma is how the chromatin fiber is folded and how this gives rise mainly to condensed chromatin domains. An immediately related question is how transcriptionally active chromatin is positioned exclusively in the perichromatin region and how nascent, replicated DNA is in the same compartment. Another enigma is the function of the large amount of RNA that never leaves the nucleus. A solution to this question may come from ongoing work on the function of many types of non-protein coding RNA, including, for instance, gene controlling microRNAs and what appears to be structural RNAs, such as Xist (Clerc and Avner, 2003). The association of intranuclear lipids with active chromatin is also intriguing. We expect that this issue of Biology of the
Cell will contribute to the generation of new ideas and will be a valuable support for further work on functional architecture of the nucleus.

References


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