# Nuclear domains

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*Journal of Cell Science 114, 2891-2893 (2001)*


The mammalian cell nucleus is a membrane-bound organelle that contains the machinery essential for gene expression. Although early studies suggested that little organization exists within this compartment, more contemporary studies have identified an increasing number of specialized domains or subnuclear organelles within the nucleus (Lamond and Earnshaw, 1998; Spector, 1993). In some cases, these domains have been shown to be dynamic structures and, in addition, rapid protein exchange occurs between many of the domains and the nucleoplasm (Misteli, 2001). An extensive effort is currently underway by numerous laboratories to determine the biological function(s) associated with each domain. The accompanying poster presents an overview of commonly observed nuclear domains.

The nucleus is bounded by a **nuclear envelope**, a double-membrane structure, of which the outer membrane is contiguous with the rough endoplasmic reticulum and is often studded with ribosomes. The inner and outer nuclear membranes are fused together in places, forming **nuclear pores** that serve in the transit of materials between the nucleus and cytoplasm (Stoffler et al., 1999). The nuclear pore complex has been shown to have a remarkable substructure, in which a basket extends into the nucleoplasm. The **peripheral nuclear lamina** lies inside the nuclear envelope and is composed of lamins A/C and B and is thought to play a role in regulating nuclear envelope structure and anchoring interphase chromatin at the nuclear periphery. Internal patches of lamin protein are also present in the nucleoplasm (Moir et al., 2000). The cartoon depicts much of the nuclear envelope/peripheral lamina as transparent, so that internal structures can be more easily observed.

Within the nucleoplasm, the chromosomes are arranged into **chromosome territories**, and active genes are thought to reside throughout the surface of the

*(See poster insert)*

loosely packed territories (Cremer et al., 2000). Homologues do not appear to be paired in interphase mammalian nuclei. In some cell types, a band of **heterochromatin** (inactive chromatin) is observed just internal to and associated with the nuclear lamina. In addition, varying amounts of heterochromatin are also observed in more internal nuclear regions. **PcG bodies** containing polycomb group proteins (i.e. RING1, BMI1 and hPc2) have been observed associated with pericentromeric heterochromatin (Saurin et al., 1998). These domains vary in number (two to several hundred), size (0.2-1.5 μm) and protein composition. It is currently unclear whether these domains are storage compartments or are directly involved in silencing.

Pre-mRNA splicing factors are localized in a pattern of 25-50 **nuclear speckles** as well as being diffusely distributed throughout the nucleoplasm (Spector, 1993). Many of the larger speckles correspond to interchromatin granule clusters (IGCs). These clusters measure 0.8-1.8 μm in diameter and are composed of 20-25-nm diameter particles that appear connected in places. IGCs have been proposed to be involved in the assembly and/or modification of pre-mRNA splicing factors. Nuclear speckles are dynamic structures, and factors are recruited from them to sites of transcription (perichromatin fibrils). **Transcription sites** are observed throughout the nucleoplasm, including on the periphery of IGCs, as several thousand foci. In addition to being diffusely distributed, several transcription factors have also been shown to be concentrated in one to three compartments termed **OPT** (Oct1/PTF/transcription) **domains**. These domains are 1.0-1.5 μm in diameter and also contain nascent transcripts as well as other transcription factors, but they contain few, if any, factors involved in RNA processing (Grande et al., 1997; Pombo et al., 1998). The OPT domain appears in G1 phase, when it often resides next to nucleoli, and it disappears during S phase. Its function is unknown.

In many cell types, pre-mRNA splicing factors are also localized in 1-10 **Cajal bodies**, previously called Coiled Bodies (Gall, 2000). These dynamic nuclear bodies are 0.2-1.0 μm in diameter and are thought to play a role in snRNP biogenesis and in the trafficking of snRNPs and snoRNPs. Spliceosomal U1, U2, U4/U6 and U5 snRNPs, as well as the U7 snRNP involved in histone 3′-end processing, and U3 and U8 snoRNPs involved in processing of pre-rRNA, all localize to this structure. It has been proposed that these factors move through the Cajal body en route to nuclear speckles (snRNPs) or nucleoli (snoRNPs). In addition, the Cajal body has been shown to associate with histone loci as well as U1, U2 and U3 gene clusters (Matera, 1999).

**Gems** (gemini of Cajal bodies) are found in the nucleoplasm and are coincident with or adjacent to Cajal bodies, depending upon the cell line examined, and they have been characterized by the presence of the survival of motor neurons gene product (SMN) and an associated factor, Gemin2 (Matera, 1999). The cytoplasmic pool of SMN and Gemin2 has been implicated in the assembly of snRNPs, and the nuclear pool may play an additional role in snRNP maturation. Interestingly, spinal muscular atrophy, a motor neuron degenerative disease, results from reduced levels of, or a mutation in, the SMN protein.

Several factors specifically involved in the cleavage and polyadenylation steps of pre-mRNA processing (e.g. CstF and CPSF) have a diffuse distribution pattern in the nucleus and in addition are concentrated in 1-4 foci, each 0.3-1.0 μm in diameter, called **cleavage bodies** (Schul et al., 1996). These structures either overlap with or are localized adjacent to Cajal bodies. The subset of cleavage bodies that do not overlap with Cajal bodies contain newly synthesized RNA.

The **Nucleolus** is the site of rRNA synthesis, rRNA processing, and assembly of ribosomal subunits (Spector, 1993) and is perhaps the most obvious internal nuclear compartment. Most mamalian cells contain 1-5 nucleoli, each 0.5-5.0 μm in diameter. The nucleolus is differentiated into three clearly identifiable regions. The fibrillar centers (shown as green ovals within the nucleolus) are regions that are thought to be the interphase equivalent of nucleolar-organizing regions (NORs) of chromosomes. Human cells contain approximately 250 copies of rDNA located at NORs on five different pairs of chromosomes. Transcription and processing of rRNA is thought to occur within the dense fibrillar component (shown as a blue reticulum), a region that surrounds and in some cases extends between the fibrillar centers. The granular region (shown as green granules) of the nucleolus is made up of pre-ribosomal particles at different stages of maturation, as well as large and small ribosomal subunits.

The **perinucleolar compartment** (PNC) and the **SAM68 nuclear body** (Huang, 2000) have been identified as unique structures that are associated with the surface of nucleoli and are thought to play a role in RNA metabolism. They range in size from 0.25-1.0 μm in diameter, and 1-10 are observed per nucleus. The PNC contains a series of small RNAs transcribed by RNA polymerase III and several RNA-binding proteins, including poly-pyrimidine-tract-binding (PTB) protein. SAM68 nuclear bodies contain members of a group of RNA-binding proteins that contain a GSG domain, also called the STAR (signal transduction and activation of RNA) domain, which is a 100-residue sequence highly homologous to the KH domain found in hnRNP K. Although the functions of the PNC and SAM68 nuclear bodies are unknown, both of these structures are predominantly found in cancer cells, and they are rarely observed in primary cells.

**PML bodies** (Maul et al., 2000) vary in size from 0.3 μm to 1.0 μm in diameter, and a typical mammalian nucleus contains 10-30 of these structures. PML bodies have also been called ND10, PODs (PML oncogenic domains) and Kr bodies. In addition to the PML protein, several other proteins, including Sp100, SUMO1, HAUSP and CBP, have been localized to this nuclear domain in addition to being diffusely distributed in the nucleoplasm. PML bodies have been suggested to play a role in aspects of transcriptional regulation and appear to be targets of viral infection.

Interestingly, individuals suffering from acute promyelocytic leukemia (APL) have a t(15,17) translocation, in which the the *PML* gene is fused to the gene that encodes the α-retinoic acid receptor, which results in the production of a fusion protein. Cells from these individuals exhibit a break-up of PML bodies into a large number of smaller domains, which are scattered throughout the nucleoplasm. Treatment with retinoic acid, which results in these individuals going into remission, also results in a reformation of typical PML bodies.

In addition to the above domains generally observed in mammalian nuclei, other domains that are specific to cell type or physiological state have also been reported. For example, GATA-1 nuclear bodies containing GATA transcription factors have been observed in murine haemopoietic cells (Elefanty et al., 1996). However, these domains are not active in transcription. HSF1 foci containing the transcription factor, heat shock factor 1, have been observed in nuclei of cells that have been subjected to heat shock, however; these domains do not coincide with *HSP70* or *HSP90* transcription sites (Jolly et al., 1997).

The above text provides an expanded legend to the accompanying poster; it is not meant to serve as a review of primary research papers, and as such much of the primary literature has not been cited here. Readers are encouraged to access the cited reviews in order to locate the primary research papers on particular nuclear bodies. I thank Jim Duffy for his outstanding artistic skills in developing the cartoon, and the following individuals who provided immunofluorescent images for this poster: Mark Frey and Greg Matera (Cajal body and Gem), Paul Mintz (RNA polymerase II transcription factor, nucleoli, peripheral nuclear lamina, perinucleolar compartment, PML body, nuclear speckles), Ana Pombo (OPT domain), Stéphane Richard (Sam68 nuclear body), Thomas Ried and Evelin Schröck (chromosome territory). In addition, I thank Edith Heard, Greg Matera and members of my laboratory for their insight and useful discussions. Research in my laboratory is funded by NIH/NIGMS 42694-12.

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