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Editorial overview: The cell nucleus: Dynamic interplay of shape and function

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The nucleus has long fascinated cell biologists, due both to its conspicuous appearance and to its inclusion of the chromosomal DNA, making it the primary site of genome duplication and gene expression. While we have some grasp on the biochemistry of many individual nuclear processes, we are still learning how they are regulated and coordinated with each other. The emergent picture suggests that the spatial organization of the nucleus is both highly dynamic and functionally important at many levels, including chromosomal organization, nuclear bodies and the composition of the nuclear envelope (NE). Subtle changes in chromosomal or nuclear organization can have profound effects, for example influencing cell fate and differentiation, but also leading to disastrous outcomes when dysregulated in disease states. This series highlights recent progress in understanding the principles underlying nuclear organization, and our nascent understanding of how they impact cell and organismal physiology.

Some of the most active questions in nuclear cell biology concern how chromosomes are arranged within nuclei and how chromosome organization impacts genome function. As discussed by [Serizay and Ahringer](#), chromosomes are not only compartmentalized into active and inactive nuclear zones, termed A and B compartments, but also constrained within topologically associating domains (TADs), that are further structured into chromatin loops. Important questions concern how boundary factors such as CTCF (CCCTC-binding factor) define TAD structures, as well as how extrusion factors such as the Cohesin complex facilitate loop dynamics. As discussed by [Shay](#), telomeres at the ends of linear chromosomes form interstitial telomere loops that alter gene expression at distal genomic regions. Importantly, these structures may be disturbed as telomeres progressively shorten with chronological age in dividing somatic cells, as well as in human laminopathies and telomeropathies that show precocious telomere shortening, potentially linking age-associated pathology to the remodeling of chromosome organization. Moreover, as discussed by [Fu et al](#), DNA replication is closely linked to the assembly of chromosomal compartments and TADs. This linkage not only reflects the dependence of replication timing on epigenetic marks within domains, but also may promote propagation of marks and domain structures to daughter cells.

Closely related questions concern how genomes are maintained within the cell cycle and how chromosomal structures are propagated and remodeled as cells grow and divide. In addition to its role in loop extrusion, Cohesin links sister chromatids from the time of DNA replication until their separation in anaphase. This linkage facilitates both homologous recombination (HR) during interphase and accurate chromosome segregation during mitosis. As discussed by [Morales and Losada](#), the establishment and dissolution of sister chromatid cohesion are both closely regulated; the former involves close coordination with the S phase DNA replication machinery, and the latter involves multiple safeguards to accurately time the release of sisters from each other. Depending on their status within the cell cycle and the formation of linked sister chromatids, cells respond differently to DNA damage, such as double-strand breaks: Cells in G₂ phase prefer HR because it allows error-free repair, but G₁ cells must generally use non-homologous end joining (NHEJ) because they lack replicated sister chromatids. [Murray and Carr](#) discuss how cells appropriately choose and activate these alternative pathways through the action of cyclin-dependent kinases and cell cycle-regulated ubiquitin ligases. Chromatin assembled at active human centromeres is marked by CENP-A containing nucleosomes, and the highly selective processes that underlie CENP-A deposition are a topic of intense investigation. As discussed by [Srivastava et al.](#), CENP-A deposition is a tightly regulated through direct post-translational modification of CENP-A nucleosomes and pre-nucleosomal complexes, of the CENP-A deposition machinery and of histones within existing centromeres. As discussed by [Hara and Fukagawa](#), kinetochore formation at prometaphase centromeres and postmitotic kinetochore disassembly involve remodeling of one of the cell's most complex protein machines, whose activity is critical for accurate chromosome segregation. Recent findings show in detail how kinetochore re-organization at mitotic entry and exit is facilitated by phosphorylation and de-phosphorylation of kinetochore components.

Importantly, processes of genome maintenance can fail, frequently leading to cascades of events that adversely impact cell and organismal viability. Anaphase chromosome segregation defects can cause cell death or the production of cell lineages with chromosomal aberrations that are characteristic of cancer cells. As discussed by [Bizard and Hickson](#), ultrafine anaphase bridges (UFB) arise from persistent entanglement of sister chromatids. UFBs frequently occur at a defined subset of genomic loci; they are recognized and actively resolved by cellular machinery. Yet, the fact that UFBs are observed in a relatively large fraction of anaphase cells raises intriguing questions about whether they have non-pathological roles in genome maintenance. On the other hand, bulky anaphase defects, including chromosome bridges and lagging chromosomes are more obviously pathological. As discussed by [Hatch](#), lagging or fragmented chromosomes from defective anaphase events induce the formation of micronuclei whose NE is particularly susceptible to rupture. Loss of NE integrity abolishes compartmental distinctions between the nucleoplasm and cytosol, potentially resulting in chromosome fragmentation and activation of innate immune responses. Related NE defects may contribute to the pathologies found in cancers, laminopathies, and autoinflammatory diseases.

Moreover, genomic disruptions that drive aneuploidy and chromosome instability (CIN) produce intratumor heterogeneity in patients that allows clonal selection amongst genetically, chromosomally and epigenetically distinct cell populations in response to

pressures such as chemotherapy treatment. [Targa and Rancati](#) discuss how these selection events shape cancer genomes, linking genomic instability and intratumor heterogeneity to poor prognosis, therapy failure and elevated rates of metastasis. Since aneuploid genomes are themselves more unstable than euploid karyotypes, they can establish degenerate loop of genetic and karyotypic instability, accelerating cancer progression.

The nucleus not only organizes and spatially constrains the genome but also controls its accessibility to the cytoplasmic contents through gating at nuclear pores. As discussed by [Ça atay and Chook](#), much of the traffic through nuclear pores is facilitated by Ran GTPase-dependent nuclear transport receptors called Karyopherins. Mis-regulation of Karyopherins may have an important impact in human diseases, particularly cancer. Changes in Karyopherins alter the localization and physiological levels of tumor suppressors, proto-oncogenes and other macromolecules, potentially promoting tumorigenesis and altering drug sensitivity of cancer cells. Karyopherin-mediated transport is inhibited in response to some physiological conditions, particularly heat stress. At the same time, it is critical for normally cytoplasmic 70-kDa heat shock proteins (Hsp70s) to enter the nucleus, where they act as both chaperones and regulators of gene expression. As discussed by [Imamoto](#), Hsp70s rely on a novel Ran-independent receptor called Hikeshi, which is essential to organismal survival. As discussed by [Heald and Gibeaux](#), the nucleus, chromosomes and mitotic spindle scale with cell size. This scaling is important for nuclear organization and maintenance of an appropriate nuclear-cytoplasmic ratio during interphase, and for correct spindle orientation and chromosome segregation during mitosis. Notably, emergent evidence suggests that the Ran pathway is important for control of nuclear volume, particularly through nuclear lamina organization, which in turn impacts the compaction level of chromosomes during mitotic condensation.

As discussed by [Gerace and Tapia](#), the nuclear lamina is also critical for a range of signaling pathways that impact cell behavior and differentiation. Nuclear lamina disruption causes a spectrum of human diseases, collectively termed laminopathies. Recent findings show not only direct interactions of signal transduction pathway components and transcriptional regulators with the lamina, but also coupling of the lamina to the cytoskeleton through the LINC complex and modulation of actin assembly. As discussed by [Zavolan and Kanitz](#), cell behavior and differentiation are further established and maintained through both transcriptional and epigenetic networks and through conserved RNA splicing and post-transcriptional regulatory pathways that control the establishment and maintenance of cell identity. Moreover, the specificity splicing factors are likely critical for somatic cell reprogramming, and the expression patterns of these splicing factors during reprogramming suggest their manipulation may be instrumental to improving the overall efficiency of this process. As discussed by [Corbett](#), mutation of RNA binding proteins that mediate key steps in post-transcriptional regulation of gene expression cause a variety of human diseases. Surprisingly, these diseases often show remarkably tissue specific phenotypes despite the ubiquitous expression of the underlying RNA binding proteins, suggesting either that processes controlled by the mutant factor are particularly active within the target tissue or that the properties of the tissue render it particularly sensitive to process disruption.

The past few years have also brought major changes in our understanding of how sub-nuclear structures are formed. The nucleolus is the largest nuclear sub-compartment, that has an established role as the site of early steps of ribosome biogenesis, as well as important roles in the assembly of non-ribosomal ribonucleoprotein complexes, regulation of cell cycle progression and sensing of environmental stress. As discussed by [Németh and Grummt](#), nucleolar architecture reflects a liquid droplet-like behavior that is closely linked to transcription-dependent changes in nucleolus-associated chromatin and is highly impacted by a variety of external cues and stresses. As discussed by [Lallemand-Breitenbach and de Thé](#), PML nuclear bodies are sites of SUMO-dependent ubiquitination/degradation and have been proposed to have important roles in chromatin remodeling, telomere biology, senescence and viral infections. As with nucleoli, PML bodies form as layered structures through networks of low-affinity interactions. A key feature of this organization is the condensation of SUMO-bound proteins into liquid-like droplets. This structure renders PML bodies dependent upon SUMO conjugation, allowing them to respond rapidly and dynamically to stress.

Finally, arguably the most critical task in genome maintenance occurs during meiosis, when the genome is passed between generations. Meiosis employs a distinct cell cycle pattern to generate haploid gametes, with two cell divisions but only a single round of DNA replication. As discussed by [Burke](#), rapid telomere-led chromosome movements during first meiotic prophase promote alignment and pairing of homologous chromosomes. To accomplish this task, forces generated by the cytoskeleton are transmitted across the NE through LINC complexes. In addition to force transduction, LINC complexes play important roles in the fidelity of homologous chromosome recombination. The mitotic divisions are a key point of evolutionary selection, particularly during female meiosis where only one of the four meiotic products will become the egg. As discussed by [Kursel and Malik](#), this leads to a competition between chromosomes, resulting in a phenomenon that has been termed meiotic drive. Recent evidence has helped to explain these events mechanistically at the level of centromere structure and polarized meiotic spindle assembly.

In sum, this series reviews recent progress on our understanding of diverse nuclear structures and molecular processes, their impact throughout the cell cycle, and their abnormal role in disease.

Biographies

Mary Dasso obtained her Ph.D. from the University of Cambridge. She pursued postdoctoral work at the University of California, San Diego, where she studied control of mitotic progression. She is currently a senior investigator at the NIH, where her group studies non-canonical functions of the nuclear transport machinery.

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