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# Editorial overview: Cell nucleus: The nucleus: a dynamic organelle

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The nucleus is perhaps the defining feature of 'eukaryotes' (Greek 'eu-' (with) '-karyon' (kernel, nucleus)), and the emperor of all eukaryotic organelles in terms of scale and complexity of organization. It is, of course, the repository for almost all genomic information, encoded in DNA sequences wrapped into chromatin as discrete polymer packages termed chromosomes, surrounded in turn by a double-membrane nuclear envelope (NE). Our investment in genomics in humans and other eukaryotes has been rightly huge; however, the return has been slow, as we discovered that sequence assemblies alone reveal little about how genetic information is utilized. Instead, genome functions are greatly influenced by processes that control nuclear and chromosome architecture and dynamics — chromatin factors and modifications, epigenetic mechanisms, and pathways for controlling transport of molecules into and out of the nucleus.

Moreover, the genome is not just a computer that reads software — rather, in the nucleus we cannot separate the control system from the machinery. For example, DNA not only provides the genetic code but also forms the dynamic scaffold for nuclear structures, and the way chromatin packaging proteins are modified can also be part of the heritable code. A huge portion of the eukaryotic cellular machinery is involved in nuclear maintenance and function, such that likely over one-third of all proteins, and almost all RNA and DNA, make the nucleus an integral part of their lifestyle in the cell. Therefore, if we ever want a full return on our investment, we must now devote resources to fully understand how the nucleus functions as an organelle, actively manages the hierarchical organization, expression, and communication across the genome, in both healthy and diseased cells. The Opinions here reflect this changing view of the nucleus as an organelle; not a passive repository for genetic information, but an active, dynamic superstructure whose processes dictate how that information is organized, accessed and used.

The Opinions presented here consider recent findings on the spatial and temporal organization of chromatin, the structure and dynamic organization of the nuclear periphery, and the mechanisms and regulation of nucleocytoplasmic exchange. As reflected in these various articles, our understanding of the architecture of the nucleus, specifically the 3D localization of genomic regions, whole chromosome and sub-chromosome domains, and nuclear bodies or 'factories' associated with transcription, replication and DNA repair, has advanced considerably in recent years due to important technological advances. They also discuss how many parts of the nucleus have multiple and dynamically changing functionalities, involving the rapid

re-purposing and re-localization of assemblies and processes once considered to have only one set of defined roles.

We start at the beginning of the nucleus' story, where Devos *et al.* discuss how valuable insights into the nucleus' evolutionary origins can be gained by comparative studies. By contrasting nuclear architectures in familiar fungal and vertebrate 'model' systems with those in evolutionary distant eukaryotic groups, hints are emerging with respect to the prokaryotic ancestors of some key nuclear components. The nucleus appears to have formed as an extension of an evolving internal membrane system along with the Golgi and ER, first as an open reticulum surrounding the chromatin and later developing a trafficking system that sealed the nucleus and differentiated its contents from the cytoplasm. The 'protocoatomer hypothesis' suggests that this process involved the repurposing of early membrane coating complexes into the structural and trafficking mechanisms that defined these different organelles. Evidence for this idea can be found buried in the heart of the nuclear pore complex (NPC), the sole mediator of trafficking across the NE, and thus between the nucleus and cytoplasm. Trafficking is mediated by a host of protein transport factors that recognize cognate cargoes and chaperone them through the NPC. The NPC and transport factors are surprisingly well conserved across all eukaryotes and contain the signature structures of coating complexes, supporting the protocoatomer idea and indicating that once its basic architectures and mechanisms were defined, they have remained stable through the last billion years of eukaryotic evolution with only some lineage-specific areas of divergence. By contrast, the nuclear lamina — the scaffold that stabilizes the NE and anchors key regions of chromatin to the nuclear periphery — varies considerably among the major eukaryotic lineages, though the reasons for this evolutionary complexity and architectural flexibility remain unclear.

The spindle is another example of a nuclear-associated structure with complex evolutionary origins that may have involved centriole-like systems that organized both the flagellum and spindle. These later duplicated into two separate structures, specialized for organizing either the flagellum/cilia or spindle, the latter retaining a core set of proteins involved in building and stabilizing microtubules as well as motors to manipulate chromosome separation during cell division. Indeed, the precise composition of the spindle, and its structural and functional relationship with other nuclear-associated structures, is a matter of both ongoing debate and active research. As Schweizer *et al.* describe, a number of proteins more traditionally associated with other roles in the nucleus may also augment the microtubule scaffold of the spindle with a dynamic 'spindle matrix'. This includes components normally associated with the NPC and lamina, which may be 'moonlighting' at the spindle during mitosis, when their normal roles are suspended. However, some degree of nucleocytoplasmic partitioning is maintained in the spindle even in the absence of traditional nuclear structures including the NE, indicating that these components may still retain their segregationist roles even in this alternate environment.

Mitosis, though, is not the only cellular process that can significantly alter and regulate the overall architecture of the nucleus. Nuclear morphology can differ strikingly among the eukaryotes, and even between different tissues in a single organism. As discussed in Jevtić *et al.*, structural components of the nuclear periphery, such as the lamina and associated assemblies, play a major role in determining nuclear shape, as do forces acting on the nucleus from the cytoplasm. However, much of how the nucleus maintains its morphology and volume is still not well understood, though clearly it is an exquisitely controlled process, and numerous disease states seem intimately linked to alterations in nuclear morphology.

One of the more surprising findings in recent years has been the demonstration that forces generated by cytoplasmic skeletal components, such as microtubules and actin, can be transmitted to inside the nucleus and act to regulate nuclear positioning and meiotic chromosome movements/pairing. Luxton and Starr review recent findings about LINC complexes, composed of SUN/KASH proteins, that together span the nuclear envelope and thereby directly link cytoplasmic force generation to nuclear dynamics. In particular, new research has shown that the KASH family of proteins, which are located in the outer nuclear envelope, interact with a wide spectrum of cytoplasmic elements, including microtubule motors, actin and myosin, intermediate filaments, and RanGAP. These new insights hold promise for a deeper molecular understanding of LINC complexes and force generation/mechanics in the nucleus, information that will contribute to diagnosis and treatment of human diseases associated with LINC complex mutations, such as autism, hearing loss and cancer.

The NPCs stand at the border of the nucleus and are seen as its 'gatekeepers', being perhaps the most prominent NE components. The major roles NPCs play in both the flow of information into and out of the nucleus, and in the regulation of gene expression, are the focus of three Opinion articles. Mor *et al.* discuss the different factors that mediate each of the multiple transport pathways that import and export macromolecules across the NE. A new understanding is emerging into how defects at various levels of the transport machinery — from the signals in cargos being recognized by transport factors, through the transport factors themselves, to the NPC itself — are at the root of many of the most important viral diseases and