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Invited Mini Review

Nuclear structures and their emerging roles in cell differentiation and development

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The nucleus, a highly organized and dynamic organelle, plays a crucial role in regulating cellular processes. During cell differentiation, profound changes occur in gene expression, chromatin organization, and nuclear morphology. This review explores the intricate relationship between nuclear architecture and cellular function, focusing on the roles of the nuclear lamina, nuclear pore complexes (NPCs), sub-nuclear bodies, and the nuclear scaffold. These components collectively maintain nuclear integrity, organize chromatin, and interact with key regulatory factors. The dynamic remodeling of chromatin, its interactions with nuclear structures, and epigenetic modifications work in concert to modulate gene accessibility and ensure precise spatiotemporal control of gene expression. The nuclear lamina stabilizes nuclear shape and is associated with inactive chromatin regions, while NPCs facilitate selective transport. Sub-nuclear bodies contribute to genome organization and gene regulation, often by influencing RNA processing. The nuclear scaffold provides structural support, impacting 3D genome organization, which is crucial for proper gene expression during differentiation. This review underscores the significance of nuclear architecture in regulating gene expression and guiding cell differentiation. Further investigation into nuclear structure and 3D genome organization will deepen our understanding of the mechanisms governing cell fate determination. [BMB Reports 2024; 57(9): 381-387]

INTRODUCTION

The nucleus is a highly organized and dynamic organelle that plays a crucial role in maintaining cellular integrity and function. Its complex architecture, comprising chromatin and the nuclear structure, provides a tightly regulated environment for essential processes such as gene expression, DNA replication, and RNA processing. The nuclear envelope, consisting of a double lipid bilayer and nuclear pore complexes, separates the nucleus from the cytoplasm, allowing for the selective exchange of molecules and creating a unique nuclear microenvironment (1-3). Within the nucleus, chromatin is organized into distinct territories, with active and inactive regions that are dynamically regulated by epigenetic modifications and chromatin remodeling complexes. The nuclear lamina, a dense fibrillar network beneath the inner nuclear membrane, provides structural support and helps maintain nuclear shape and mechanical stability (4, 5). Additionally, sub-nuclear structures, such as the nucleolus, nuclear speckles, and Cajal bodies, serve as specialized hubs for various nuclear processes, further contributing to the functional organization of the nucleus (6-10).

Recent advances in our understanding of nuclear architecture have begun to reveal the intricate interplay between nuclear structure and cellular differentiation. As cells differentiate into specific lineages, they undergo profound changes in gene expression, chromatin organization, and nuclear morphology. The dynamic remodeling of chromatin and its interactions with various nuclear structures, such as the nuclear lamina, nuclear pore complexes, and sub-nuclear bodies, are considered to play essential roles in fine-tuning gene expression patterns during differentiation (11-15). Epigenetic modifications, including DNA methylation and histone modifications, work in concert with chromatin remodeling complexes to modulate gene accessibility and ensure precise spatiotemporal control of gene expression (16-18). Furthermore, the spatial organization of chromatin within the nucleus, as seen in particular in its interactions with the nuclear periphery and inner nuclear scaffold, has emerged as an important factor in regulating cell type-specific gene expression programs (19, 20). As our knowledge of the complex relationship between nuclear structure and cellular differentiation continues to expand, it becomes increasingly clear that the nucleus is not merely a passive container for genetic material, but rather an active and dynamic organelle that plays a vital role in determining cell fate and function.

NUCLEAR STRUCTURE AND FUNCTION

The nucleus, the commend center of the cell, is a highly structured organelle that is essential to maintain cell integrity

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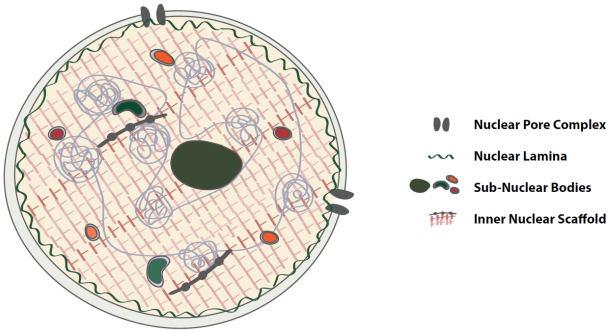

Fig. 1. Nuclear structure of a mammalian cell. The mammalian cell nucleus is composed of chromatin and functional nuclear structures. The nuclear pore complex is embedded within the nuclear envelope, while the nuclear lamina lies beneath it. Inside the nucleus, inner nuclear scaffold proteins and various sub-nuclear bodies can be found, including the nucleolus, nuclear speckles, Cajal bodies, and promyelocytic leukemia (PML) bodies.

and function (Fig. 1). The nuclear envelope, composed of a double lipid bilayer, encloses the nucleus, separating the nucleoplasm from the cytoplasm and creating a unique environment. This separation is crucial for regulating processes, such as gene expression and DNA replication, in a controlled manner. Within the nuclear envelope are large multiprotein structures called nuclear pore complexes (NPCs), which are composed of various proteins known as nucleoporins. NPCs are well-known for their crucial role in regulating the selective exchange of molecules between the nucleus and the cytoplasm, thereby facilitating nucleocytoplasmic transport (3). Recent research has expanded our understanding of NPCs by identifying their role in regulating gene expression independently of their transport functions (14). Of the two membranes of the nuclear envelope, the outer membrane is continuous with the endoplasmic reticulum, while the inner membrane is associated with the nuclear lamina, which is composed of lamin proteins (5). This structure provides mechanical support, maintaining the shape of the nucleus and organizing chromatin. Mutations in lamin proteins can lead to genetic disorders known as laminopathies, highlighting their crucial role in nuclear function (21).

Within the nucleus, DNA is packaged into chromatin, a complex of DNA and histone proteins. Chromatin exists in two forms: euchromatin, which is less condensed and actively transcribed, and heterochromatin, which is highly condensed, and in general, transcriptionally inactive. The dynamic organization of chromatin is crucial to regulate gene expression in response to developmental cues and environmental changes. Additionally, the nuclear scaffold, or nuclear matrix, is a framework of fibrous proteins that provides structural support to the nucleus, organizing its three-dimensional architecture and facilitating processes such as gene transcription and RNA processing (22, 23). This structural support is essential to maintain the shape and integrity of the nucleus, ensuring the proper functional organization of chromatin and the regulation of gene expression.

Sub-nuclear structures, or nuclear bodies, are distinct membraneless regions within the nucleus that specialize in various nuclear processes. These include the nucleolus, nuclear speckles, Cajal bodies, and promyelocytic leukemia (PML) bodies. The nucleolus is primarily involved in ribosome biogenesis, while Cajal bodies function as hubs for ribonucleoprotein particle formation and RNA metabolism (8, 10, 24). Nuclear speckles play a crucial role in the storage and modification of pre-mRNA splicing factors (7, 25). PML bodies, though their precise role remains unclear, are implicated in processes such as post-translational regulation and stress response (26, 27). These sub-nuclear bodies primarily occupy the interchromatin space and are associated with factors involved in specific functions (6), contributing to the complex and dynamic organization of the nucleus.

INTERPLAY BETWEEN NUCLEAR STRUCTURE AND CELL DIFFERENTIATION

Cellular differentiation is a highly orchestrated process that involves the precise control of gene expression to drive the specialization of cells into distinct lineages. At the core of this process lies the complex interplay between chromatin structure, nuclear architecture, and gene regulation. Chromatin undergoes extensive remodeling during differentiation, resulting in altered accessibility of genes to transcriptional machinery. Studies indicate that the three-dimensional organization of chromatin and its interactions with various nuclear structures, such as the nuclear lamina, nuclear pore complexes, sub-nuclear bodies, and nuclear scaffold, contribute to the modulation of gene expression patterns. As cells differentiate, they experience profound changes in their epigenetic landscape, chromatin conformation, and nuclear morphology that work in concert to establish and maintain cell type-specific gene expression programs. This section explores the intricate relationship between chromatin structure, nuclear architecture, and gene expression during cellular differentiation.

Epigenetic regulation and chromatin reorganization play a significant role in regulating gene expression during cell differentiation. Epigenetic modifications, such as DNA methylation and histone modifications, serve as molecular markers that can activate or silence genes, without altering the underlying DNA sequence. These modifications are critical to determining cell fate, as they enable the dynamic and reversible regulation of gene activity in response to developmental signals and environmental factors. For example, DNA methylation is typically associated with gene silencing influencing the binding of various regulatory proteins (16). Histone modifications encompass a diverse range of changes, including acetylation, methylation, and phosphorylation, which affect the chromatin compaction,

thereby modulating accessibility to transcriptional regulators. Chromatin remodeling complexes further facilitate these processes by repositioning nucleosomes, thereby altering the chromatin landscape to either expose or shield regulatory regions of the genome (17, 18). The complex coordination between epigenetic modifications and chromatin structure ensures that specific sets of genes are precisely turned on or off during the various stages of development, allowing progenitor cells to develop into specialized cell types with distinct functions.

The spatial organization of chromatin within the nucleus influences gene expression by affecting the proximity of genes to transcriptional regulators (28-30). Actively transcribed genes are typically located in the euchromatin, which is less densely packed and more accessible, whereas inactive genes reside in the heterochromatin, which is tightly packed and less accessible. The positioning of genes relative to nuclear structures also impacts their expression. Genes near the nuclear periphery tend to be transcriptionally silent, while those in the nuclear interior are often transcriptionally active. Recent studies have shown that the role of nuclear structures in the regulation of gene expression is also critical during cell differentiation and development. The 3D organization of chromatin changes dynamically during differentiation, leading to the rearrangement of gene accessibility and the activation of lineage-specific genes. Thus, the highly organized and dynamic structure of chromatin within the nucleus is essential for precise gene regulation and cell differentiation, allowing genes to be expressed at the right time and space.

To further elucidate the intricate relationship between nuclear structure and cellular differentiation, it is crucial to examine specific components of nuclear architecture. The nuclear lamina, nuclear pore complexes, sub-nuclear bodies, and the inner nuclear scaffold all play vital roles in shaping the nuclear environment and influencing gene expression during differentiation. These components contribute to the establishment and maintenance of cell type-specific gene expression programs through their interactions with chromatin and other nuclear factors. By exploring each of these elements in detail, we can gain a more comprehensive understanding of how nuclear architecture orchestrates cellular differentiation.

Nuclear lamina structure and its significance in cellular differentiation

The nuclear lamina, a dense fibrillar network that lies beneath the inner membrane of the nuclear envelope, is primarily composed of intermediate filament proteins, called lamins, which are classified into two types: A-type and B-type lamins (21, 31). Lamins and associated proteins form a filamentous meshwork, providing structural support to the nucleus and maintaining its shape and mechanical stability (5). This structural framework stabilizes the integrity of the nucleus, while also playing a crucial role in organizing chromatin, influencing gene expression, and participating in various nuclear processes, such as DNA replication, transcription, and cell cycle progression (32-35). By anchoring chromatin to the nuclear envelope, the lamina establishes distinct nuclear compartments that segregate active and inactive regions of the genome. This spatial organization is essential to maintaining gene expression patterns that are specific to cell type and function. For instance, genes that need to be silenced are often located in peripheral heterochromatin regions, where they are tightly packed and less accessible to transcriptional machinery. Conversely, actively transcribed genes are found in euchromatin regions, which are more centrally located and loosely packed, facilitating access by transcription factors and RNA polymerase.

During cell differentiation, the nuclear lamina undergoes significant remodeling to facilitate the necessary changes in the regulation of gene expression (11). Recent studies have also identified that Lamina-Associated Domains (LADs), regions of the genome that interact with the nuclear lamina, dynamically restructure during differentiation (4). This discovery has led to various investigations into the correlation between the relative positioning of genes at the nuclear lamina and the regulation of their expression. For example, nuclear lamina–genome interactions are involved in lineage commitment to cardiac and neural cells, and the relative positioning of genes to the nuclear lamina changes during the differentiation process of myoblasts (36-38). Genes located within LADs often exhibit specific epigenetic marks, such as histone H3K9 methylation, which are associated with transcriptional repression, and epigenetic modifications are involved in facilitating this process (36). In fact, experiments involving the artificial tethering of genes to the nuclear lamina have demonstrated transcriptional repression mediated by the repositioning of genes to the nuclear lamina in mouse fibroblasts (39). These findings underscore the role of the nuclear lamina and LADs in regulating gene expression through spatial organization within the nucleus, highlighting their importance in the context of cellular differentiation.

Nuclear pore complexes and their impact on differentiation processes

Nuclear Pore Complexes (NPCs) are large protein assemblies that are embedded in the nuclear envelope, serving as gateways that regulate molecular transport between the nucleus and cytoplasm. These structures are crucial for maintaining cellular homeostasis by controlling the exchange of RNA, proteins, and other macromolecules (40). Composed of multiple proteins called nucleoporins, NPCs form a cylindrical structure with a central channel that facilitates selective molecular passage. Small molecules diffuse freely through this channel, while larger molecules, such as RNA and proteins, require active transport mediated by specific receptors. Interestingly, studies have demonstrated that NPC components influence the regulation of gene expression across various organisms, independent of their primary transport function (1, 41-43). For example, Nup153, a nucleoporin, is essential for maintaining pluripotency in mouse embryonic stem cells; its depletion leads to the dere-

pression of developmental genes by affecting polycomb-repressive complex 1 (PRC1) recruitment to chromatin. Similarly, Nup98 is involved in epigenetic memory, and has been shown to associate with MBD-R2/NSL and Trx/MLL histone-modifying complexes and regulate Hox gene expression in developing flies. By interacting with transcription factors, other NPC proteins, and epigenetic factors, these components can either activate or repress the expression of a wide range of genes, including those involved in developmental processes.

The spatial arrangement of chromatin near NPCs also plays a role in regulating gene expression. Protein networks can anchor a subset of genes and their associated protein complexes to NPCs in the nuclear envelope, creating a microenvironment that allows for the distinct regulation of gene expression, such as transcriptional activation (2, 44-47). Intriguingly, the expression levels of various nucleoporins and transport proteins have been observed to vary during cell differentiation, and the expression of certain NPC components is required for cell fate determination and the differentiation process (12, 14). For instance, changes in expression levels of various nucleoporins were observed during mesenchymal stem cell differentiation (48). Moreover, during the neural differentiation of mouse embryonic stem cells, the expression of importin-α subtype transport proteins undergoes precise regulation, with shifts in importin-α subtype expression playing a crucial role in facilitating neural differentiation (49). The influence of these nucleocytoplasmic transport proteins on cellular processes, particularly cell differentiation, can be primarily attributed to the involvement of NPCs in the transport of diverse transcription factors, differentiation regulators, and pluripotency factors. As these factors are shuttled between the nucleus and cytoplasm, their spatial and temporal distribution can significantly impact gene expression patterns, and ultimately, cell fate decisions. To fully elucidate the complex roles of NPCs in differentiation, further research focusing on various stages of the process is necessary.

Sub-nuclear bodies and their associations with cell differentiation processes

Sub-nuclear bodies are specialized, membraneless structures within the nucleus that play diverse roles in regulating various nuclear functions. These structures include the nucleolus, Cajal bodies, nuclear speckles, and PML bodies, each with distinct functions. The nucleolus, one of the most noticeable structures observed in cells under phase contrast microscopy, is primarily involved in ribosome biogenesis, synthesizing ribosomal RNA (rRNA) and assembling it with ribosomal proteins to form ribosomes, which are essential for protein synthesis (10). Cajal bodies, which are distinguished by the presence of coiled threads of the marker protein coilin (50), serve as preassembly sites for transcriptosomes and contain protein components essential for the transcription and processing of nuclear RNAs, effectively functioning as hubs for ribonucleoprotein (RNP) particle formation and RNA metabolism (8, 24). Nuclear speckles, rich in pre-mRNA splicing factors and commonly identified by the marker SC35 (9), play a crucial role in the storage and modification of these factors, ensuring efficient splicing and processing of pre-mRNAs (7, 25). The precise role of other sub-nuclear bodies, such as PML bodies, remains elusive (26, 27, 51, 52). PML bodies form around the PML protein, a tumor suppressor that polymerizes into punctate structures and recruits many seemingly unrelated partner proteins. While these structures are implicated in a broad spectrum of biological processes, including post-translational control and stress response, a unifying biochemical function has yet to be clearly defined.

The composition and dynamics of sub-nuclear bodies are notably associated with cellular differentiation and development. As cells differentiate, they experience alterations in gene expression and nuclear organization, which are accompanied by changes in sub-nuclear structures. For example, when cells differentiate from embryonic stem cells to neural progenitor cell, the nucleolus undergoes dramatic changes in size and number as cells differentiate, with a general trend towards a greater number of smaller nucleoli in the differentiated cells (53-55). This change appears to reflect a decrease in ribosome biogenesis and a shift toward more specialized cellular functions. Similarly, the number of Cajal bodies varies, but tends to be higher in the early stages of embryo development and to decrease upon differentiation, which somewhat correlates with the transcriptional and metabolic activity of the cells (13, 24). In contrast, the number and size of PML bodies have been shown to vary during differentiation, as observed in hematopoietic and prostate cells, possibly reflecting their dispensable role during development (51, 56). Emerging studies demonstrate that the proximity of chromatin to nuclear speckles is associated with gene expression that can regulate cell differentiation (9, 57). For example, the chromatin architectural protein CTCF forms stress-sensitive complexes localizing to nuclear speckles during specific stages of neuronal commitment but not in differentiated neurons. The mechanism linking nuclear speckles and gene expression levels is mediated by the dynamic properties of the 3D genome architecture, where genes located closer to nuclear speckles tend to exhibit higher levels of transcription and splicing. This spatial organization is likely due to the high concentration of splicing factors within nuclear speckles, offering insights into how the nuclear environment influences gene regulation and contributes to the process of cellular differentiation.

Inner nuclear scaffold architecture and its impact on cellular differentiation

The nuclear scaffold, also known as the nuclear matrix, is a complex network of fibrogranular proteins and RNA that forms a structural framework within the nucleus of eukaryotic cells. This matrix structure was identified through a series of sequential salt extractions, detergent, and DNase treatments (58, 59). The nuclear matrix has been implicated in organizing chromatin structure by providing attachment sites for matrix attachment

regions (MARs) to MAR-binding proteins, thereby forming chromatin loops (60). Although the interaction between chromatin and the nuclear matrix was predicted to influence many biological functions, it has only recently been thoroughly investigated at the molecular level (61). Efforts to identify components of nuclear matrix proteins have led to the identification of nuclear lamins, nucleolar proteins, and inner nuclear proteins, such as heterogeneous nuclear ribonucleoproteins and nuclear matrins, which were named after their discovery as major nuclear matrix components (62). Among these, Matrin-3 has gained attention due to its abundance in the nucleus and recent studies suggesting its specific functions, emphasizing the role of inner nuclear proteins (63). Matrin-3 associates with other structural and regulatory factors in the nucleus, controls RNA processing, and coding mutations in its gene have been linked to rare genetic disorders (64-66). Very recently, the regulatory role of Matrin-3 at the chromatin level and in transcriptional control has been proposed, highlighting its more direct involvement in the regulation of gene expression, further expanding our understanding of the roles of nuclear matrix components in maintaining nuclear structure and regulating cellular processes (19, 23, 67).

While the role of nuclear membrane proteins, such as lamins, in regulating gene accessibility during differentiation has been well-established, the contribution of nucleoplasmic proteins, which constitute a large component of the inner nucleus, to chromatin remodeling during transcription and differentiation remains less explored. Studies have shown that hnRNP components, such as SAF-A/hnRNP U and SAF-B, contribute to the organization and regulation of chromatin structure (68, 69). In the context of development, Matrin-3, another inner nuclear protein, has been suggested to maintain the undifferentiated state of neural stem cells, albeit limited to morphological observations (70). A more direct relationship between inner nuclear scaffold proteins and differentiation was recently examined using Matrin-3. In erythroid cells, Matrin-3 was found to interact with architectural proteins, such as CTCF and cohesin, stabilizing chromatin structure and negatively regulating differentiation (19). This association was also observed in mouse embryonic stem cells and muscle cells, suggesting that the role of Matrin-3 in coordinating chromatin organization and gene expression during cellular differentiation may be more general (19, 20). These findings provide new insights into the complex interplay between nuclear architecture and cell fate determination, underscoring the importance of inner nuclear scaffold proteins in this process.

CONCLUSION

The intricate relationship between nuclear structure and cellular differentiation is an intriguing area of research that has gained notable attention in recent years. As evidenced by the studies discussed in this review, the nucleus is a highly organized and dynamic organelle that undergoes profound changes during the process of cellular differentiation. The complex interplay between chromatin structure, epigenetic modifications, and nuclear architecture plays a crucial role in regulating gene expression and driving cell fate decisions. The nuclear lamina, nuclear pore complexes, sub-nuclear bodies, and inner nuclear scaffold all contribute to the functional organization of the nucleus, and have been implicated in various aspects of cellular differentiation. As cells differentiate, they undergo significant remodeling of chromatin and alterations in the spatial arrangement of genes, which are mediated by interactions with these nuclear structures. Epigenetic modifications and chromatin remodeling complexes further fine-tune gene expression patterns, ensuring precise control over cell type-specific transcriptional programs.

Despite the significant progress made in understanding the relationship between nuclear structure and cellular differentiation, many questions remain unanswered. Future research could concentrate on further elucidating the molecular mechanisms underlying the dynamic changes in nuclear architecture during differentiation, as well as the specific roles of individual nuclear components in regulating gene expression and cell fate. Emerging approaches for future investigation include the use of degrader molecules for dynamic regulation of protein expression and the application of high-resolution chromatin capture techniques. These advanced approaches could provide unprecedented insights into the temporal dynamics of nuclear reorganization and the fine-scale chromatin interactions that occur during cellular differentiation. As our knowledge of the nucleus continues to expand, it will deepen our understanding of the fundamental principles governing cellular differentiation, while also potentially leading to the development of novel therapeutic strategies for diseases associated with aberrant nuclear structure and function. The study of nuclear structure and its role in cellular differentiation therefore represents an exciting and rapidly evolving field that promises to provide new insights into the complex mechanisms underlying cell fate determination and organismal development.

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CONFLICTS OF INTEREST

The author has no conflicting interests.

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