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The Functions of the Nuclear Envelope in Mediating the Molecular Crosstalk between the Nucleus and the Cytoplasm

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Abstract

Recent studies of the nuclear envelope (NE) have emphasized its role in linking the nuclear and cytoplasmic compartments of mammalian cells. The inner face of the NE is bound to chromatin and this interaction is involved in regulating DNA replication and transcription. The outer face of the NE binds to different components of the cytoskeleton, and these interactions are involved in nuclear positioning. Many disease causing mutations in genes encoding NE proteins cause significant changes in nuclear architecture and cytoskeletal interactions with the NE. These mutations are also providing important new insights into nuclear-cytoplasmic interactions.

Introduction

During interphase of mammalian cells, the nuclear envelope (NE) establishes and maintains the overall shape, size and mechanical integrity of the nucleus. At the nuclear periphery, chromatin is anchored to the inner aspect of the NE, which provides a mechanism for the spatial control of DNA replication and transcription [1]. Recent studies have shown that the cytoskeletal systems are attached to the cytoplasmic face of the NE which appears to mediate interactions between the nucleus and the cytoplasm [2]. These interactions facilitate cellular processes including nuclear positioning and centrosome orientation during cell migration [3••].

Other insights into the functions of the NE have been derived from studies of disease mutations in genes encoding NE proteins, particularly the nuclear lamins. Some mutations frequently cause significant changes in nuclear shape, chromatin organization and gene expression [4], and they also modulate nuclear positioning and centrosome orientation [5•]. These changes reflect nuclear-cytoplasmic interactions.

This review focuses on the functions of the NE in mediating the molecular crosstalk between the nucleus and the cytoplasm.

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The Nuclear Envelope Links the Nuclear and Cytoplasmic Compartments of Mammalian Cells

The NE is comprised of inner and outer nuclear membranes (INM and ONM), nuclear pore complexes (NPCs) and the nuclear lamina. Approximately 80 INM and ONM proteins and ~ 50 NPC proteins (nucleoporins) have been identified in mammalian cells [6•,7]. The major proteins of the lamina are the type V intermediate filament proteins, the A-type lamins (LA and LC) and the B-type lamins (LB1 and LB2). LA and LC are derived from a single gene (*LMNA*) by alternative splicing and are expressed only in differentiated cells. LB1 and LB2 are encoded by *LMNB1* and *LMNB2*, respectively, and at least one of them is expressed in all cells throughout development [8]. Lamins within the lamina form filamentous structures [9,10] composed of separate but interacting A- and B-type lamin meshworks [11•]. The lamins also bind to other NE proteins, including some NPC and INM proteins (Fig. 1). These protein-protein interactions are critically important in regulating the proper assembly of the NE. For example, LB1 silencing induces changes in the LA/C meshworks creating LA/C rich microdomains devoid of LB1, LB2 and NPCs [11]. LA/C is also required for the proper localization of INM proteins such as emerin [12–14].

All of the lamins, as well as some nucleoporins and INM proteins, interact with chromatin and play a role in the regulation of transcription and DNA replication [1]. For example, some transcriptionally active genes are associated with nucleoporins at the nucleoplasmic face of NPCs [15], while silenced genes are tethered to the lamina [16–18]. However, these gene silencing effects associated with the lamina may be gene specific [19,20]. In addition, both the A- and B-type lamins and the lamina-associated polypeptide 2β (LAP2β) are involved in the initiation and elongation phases of DNA replication [21–23].

There is also evidence that some ONM proteins interact with specific proteins of the cytoskeletal systems (Fig. 1). These include the nesprins which span the ONM and components of the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex. The nesprin C-terminus located in the luminal region separating the ONM and INM contains a KASH (Klarsicht/ANC-1/Syne Homology) domain which binds to the SUN (Sad1p and UNC-84) domain proteins which span the INM [2]. At the cytoplasmic face of the ONM, the nesprins appear to bind directly to actin, associate with microtubules through interactions with dynein and kinesin, and interact with intermediate filaments via plectin (Fig. 1–2) [2,24]. At the nucleoplasmic face of the INM, there is evidence that SUN1 binds directly to LA [2]. It has also been shown that the LINC complex in association with LA is required for controlling nuclear positioning and centrosome reorientation during cell migration [3,5,25]. LB1 is also involved in anchoring the nucleus to the cytoskeleton through nesprin-1 and -2 [26].

The Nuclear Envelopathies/Laminopathies Shed New Light on Nuclear-Cytoplasmic Interactions: Nuclear Shape, Chromatin Organization and Cytoskeleton-NE Interactions

Nuclear envelopathies/laminopathies are a large group of human diseases caused by mutations in genes encoding NE proteins such as the nucleoporins, INM and ONM proteins and the lamins (Table 1). Frequently cells from patients with these diseases exhibit abnormal nuclear shapes, alterations in chromatin organization and changes in the cytoskeletal systems [4,8]. For example, mutations in the gene encoding the INM protein emerin cause X-linked Emery-Dreifuss muscular dystrophy (XL-EDMD). Nuclei in XL-EDMD patients' muscle cells are misshapen due to the formation of nuclear blebs or lobulations [41]. In contrast, nuclei in mature neutrophils are normally hyperlobulated [56]. Interestingly,

mutations in another INM protein lamin B receptor (LBR) cause Pelger-Huët disease which inhibits hyperlobulation of nuclei and the proper maturation of neutrophils [44,57]. In the case of ONM proteins, there is a mutation resulting in a deletion of the KASH domain in nesprin-1, which causes arthrogryposis multiplex a disease resulting in abnormal joint contractures [45]. A model of cardiomyopathy has been described in mice expressing a nesprin-1 mutant missing the KASH domain, and the cardiocytes of these mice have abnormally elongated nuclei [46, 47•]. Furthermore, the knockout and silencing of nesprin-2 giant, another ONM protein which interacts with SUN domain proteins, induce nuclear blebbing in both mouse and human cells [58]. Since nesprins interact with cytoskeletal filaments such as actin and intermediate filaments, these findings suggest that the determination of nuclear shape is complex and to a great extent dependent on the interactions between the NE and the cytoskeletal systems.

Most information regarding the relationships between the NE, chromatin and the cytoskeletal systems comes from studies of the laminopathies, which represent the largest group of nuclear envelopathies. These are caused by hundreds of different mutations, mainly in human *LMNA* [59]. These mutations cause a remarkable number of different diseases including autosomal EDMD and Limb Girdle muscular dystrophy, dilated cardiomyopathy, lipodystrophy, Charcot-Marie Tooth disease, and premature aging diseases such as Hutchinson-Gilford Progeria Syndrome (HGPS, progeria) [59]. The structure of the lamina is altered by some mutations causing autosomal dominant EDMD (AD-EDMD). Nuclei of these patients' cells have an enlarged lamin meshwork within the lamina known as honeycomb structures [27]. Other AD-EDMD mutations induce the formation of LA/C foci in the nucleoplasm [27] and block nuclear positioning and centrosome orientation [5•], suggesting that the interactions between the NE and the cytoskeletal systems are disrupted. The effects of these mutations on nuclear shape and chromatin organization vary depending on the locations of point mutations or deletions. For example, the HGPS mutation G608G (progerin/LAΔ50) located in the non-α-helical C-terminal domain of LA, causes an abnormal thickening of the lamina, nuclear blebbing, and abnormal distributions of B-type lamins and NPCs in skin fibroblasts (Fig. 3) [34••]. In addition, there is a dramatic loss of peripheral heterochromatin, accompanied by a decrease in histone methylation and acetylation of lysine residues in histones H3 and H4 and in gene expression [60, 61•, 62]. The atypical progeria mutation, E145K, located in the α-helical central rod domain of LA/C causes abnormal polymerization of LA/C, nuclear lobulations resulting in flower-shape nuclei, alterations in pericentric heterochromatin, abnormally clustered centromeres, and mislocalized telomeres [36]. Another atypical progeria mutation in *LMNA*, S143F, causes numerous blebs and lobulations of the NE as well as an enlarged lamin meshwork within the lamina [35]. Interestingly this phenotype appears to be rescued by the expression of nesprin-2 giant [35]. LA/C knockout mouse embrionic fibrobrasts (MEFs) and myocytes derived from LA/C knockout mice also display blebbed nuclei with displaced and fragmented heterochromatin [12,63].

Nuclear blebs can also be induced by silencing LB1 expression or by expression of a deletion mutation of LB1 in mice [11,64,65]. These nuclear blebs contain gene-rich euchromatin and the activated form of RNA polymerase II (pol II) but are transcriptionally defective, suggesting that pol II is stalled [11]. MEFs expressing a deletion mutant of LB1 contain nuclear blebs and exhibit changes in gene expression [66]. Further support for a role of NE proteins in transcription comes from the finding that they bind to transcriptional factors. For example, LA binds to MOK2, SREBP1 and c-Fos, and emerin binds to GCL and Lmo7 [67–71].

Taken together, this wide range of investigations provides a framework to describe in more detail the structural and functional linkages between the NE and chromatin on the one hand and with the NE and the cytoskeletal systems on the other (Fig. 1).

Mechanotransduction between the Nucleus and the Cytoplasm

Emerging evidence suggests the interesting possibility that nuclear shape may be regulated in part by the mechanical properties of the NE and the cytoskeletal systems attached to it. In support of this it has been found that mechanical stress exerted at the outer cell surface causes changes in nuclear shape possibly through the LINC complex [72•, 73••]. The intrinsic mechanical properties of the NE or the entire nucleus may also affect nuclear shape. For example, LA/C knockout MEFs have blebbed nuclei, which are “softer” relative to those of WT MEFs when assayed by mechanical strain [12, 74•]. In the case of HGPS, skin fibroblasts from the patients have “stiffer” nuclei with a thicker lamina compared to normal skin fibroblasts [34,75,76]. On the other hand, emerin knockout MEFs have normal nuclear mechanics but there are significant changes in nuclear shape [77], suggesting that changes in nuclear mechanics are not always coupled to changes in nuclear shape.

It has been proposed that the interactions between the plasma membrane and the cytoskeletal systems regulate gene expression in response to mechanical stress initiated at cell surfaces [78]. Such a mechanism for mechanotransduction is particularly interesting because mechanically-based signal propagation is faster than chemically based-diffusion [78]. Mechanotransduction appears to involve integrins in the plasma membrane interacting with cytoskeletal filaments such as actin and/or intermediate filaments. In turn these cytoskeletal components can transduce mechanical forces to the nucleus [79–81]. In support of this, endothelial cells subjected to shear stress exhibit rapid changes in gene expression and the organization of cytoskeletal intermediate filaments [82•,83]. There is also evidence that some NE proteins are involved in gene regulation in response to mechanical stress. For example, LA/C or emerin knockout MEFs subjected to mechanical strain are defective in expressing mechano-sensitive genes [74,77]. On the other hand, recent studies have shown that when the LINC complex is disrupted by the expression of a dominant negative KASH domain, the regulation of mechano-sensitive genes is normal in response to mechanical stress [73]. Although this result is not conclusive, it also suggests that interactions between the NE and the cytoskeletal systems may not be required for all aspects of mechanotransduction. One possibility to explain such findings is that other signaling pathways such as the propagation of chemical signals may act synergistically with mechanotransduction to facilitate interactions between the nucleus and the cytoplasm. Such synergistic interactions could provide compensatory mechanisms to explain the response of mechano-sensitive genes in the absence of the known complexes that link the nuclear lamina with the cytoskeleton. It should be noted, however, that this area of research is in its early phases and there are likely to be numerous linkages between the lamina, the NE and the cytoskeleton that have yet to be discovered.

Outlook

Knowledge is accumulating to show that during interphase the NE mediating the interactions between the nucleus and cytoplasm are involved in regulating nuclear shape, chromatin organization, gene expression and nuclear positioning.

Over the next few years we should see an explosion of interests in the structural synergy and molecular cross talk regulating the interactions between the nuclear and cytoplasmic compartments of mammalian cells. The NE is a critically important hub facilitating these interactions as it demarcates and provides a molecular interface between these two major cellular compartments. In addition to nuclear transport mechanisms for exchanging large

molecules between the nucleus and the cytoplasm, the results to date provide compelling evidence for the presence of multiple chains of protein-protein interactions which pervade the entire cell. The following scenario can be pieced together from data derived from disparate sources. The outer surface of the plasma membrane/ECM connects with different but interacting cytoskeletal networks comprised of microtubules, intermediate filaments, microfilaments and their associated proteins. These cytoskeletal components are connected to the ONM via the LINC complex which forms transmembrane linkages to the lamina. In turn the lamina forms a complex interface between the INM and peripheral elements of interphase chromosomes. The latter are typically tethered to the lamina and the regulation of this tethering is involved in the regulation of gene expression. It is becoming more apparent that these interacting networks provide a structural framework for further defining mechanisms involved in the bidirectional propagation of signals and molecules between the nucleus and the cell surface. Sufficient components of the network are now in place to begin to speculate about what these structural pathways might be doing and how they might function. Most likely these pathways provide the cell with a complex of superhighways composed of interconnecting molecules capable of transmitting both mechanical and chemical signals from the external environment of cells to the nucleus, ultimately regulating gene expression. Of course the devil is in the detailed identification and analysis of the many molecules which undoubtedly are required for the functions of these proposed superhighways. Such knowledge is required to define functions and determining. In other words, it will be many years before we reach the same level of sophisticated structure/function relationships now in hand for some components of the NE, such as the NPCs as described.

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• of special interest

•• of outstanding interest

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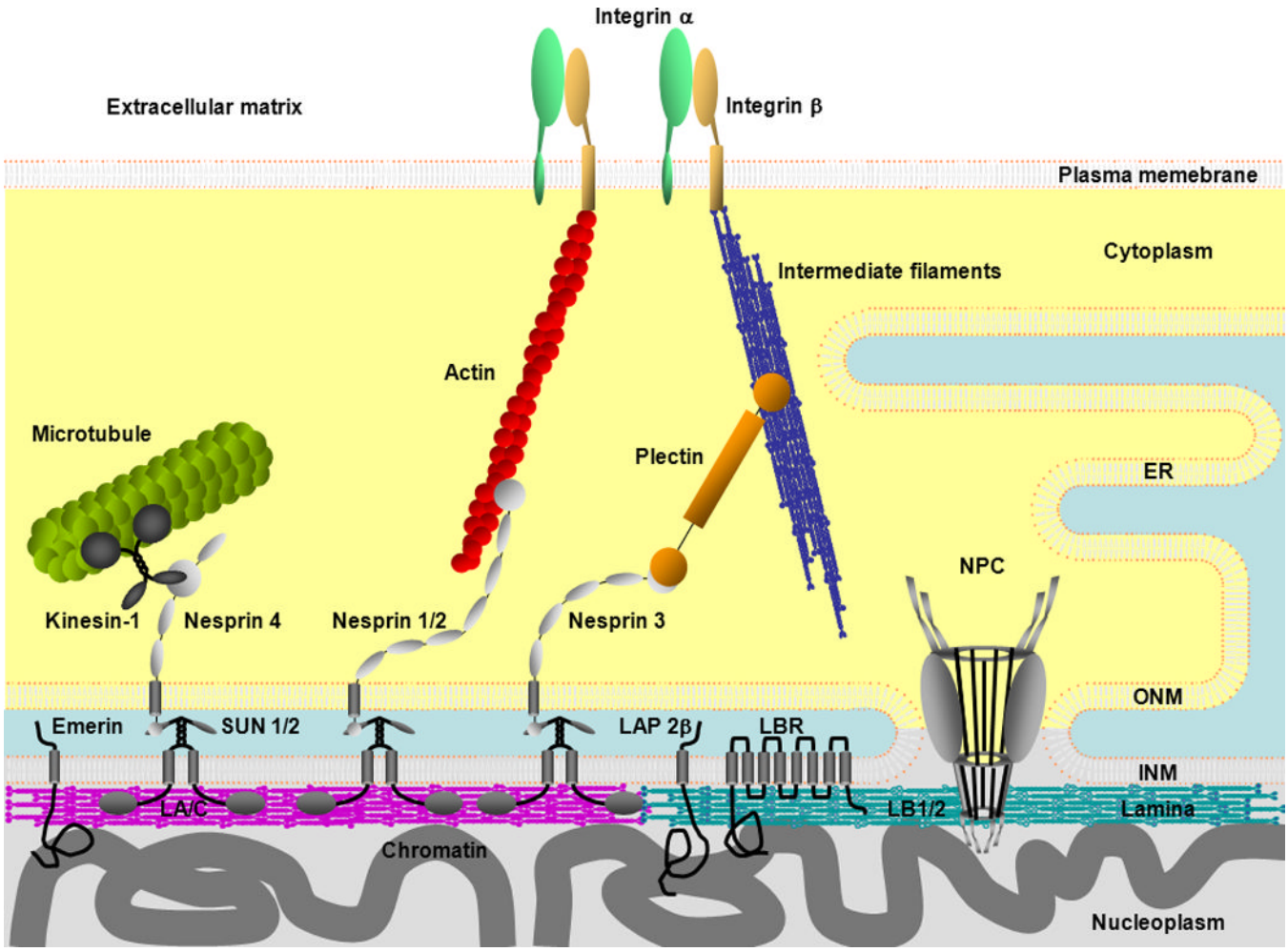

Figure 1.

An overview of nuclear envelope (NE) connections with chromatin,and the cytoskeletal systems. The NE consists of the inner and outer nuclear membrane (INM, ONM), nuclear pore complexes (NPCs) and the lamina. The ONM is continuous with the endoplasmic reticulum (ER). NPCs cross the INM, ONM, the lamina and are associated with chromatin. A-type lamins (LA, LC) and B-type lamins (LB1, LB2) in the lamina bind to INM proteins such as emerin, lamina-associated polypeptide 2β (LAP2β), lamin B receptor (LBR) and SUN domain proteins (SUN1, SUN2) in the INM. All of the lamins and some of the INM proteins interact with chromatin. SUN1 and SUN2 bind to the KASH domain of nesprins in the luminal region between the INM and ONM to form the LINC complex. Nesprins in the ONM bind to cytoskeletal filaments such as actin, microtubules and intermediate filaments (IFs) directly or indirectly through plectin or kinesin. Actin and IFs are associated with the plasma membrane through integrin complexes.

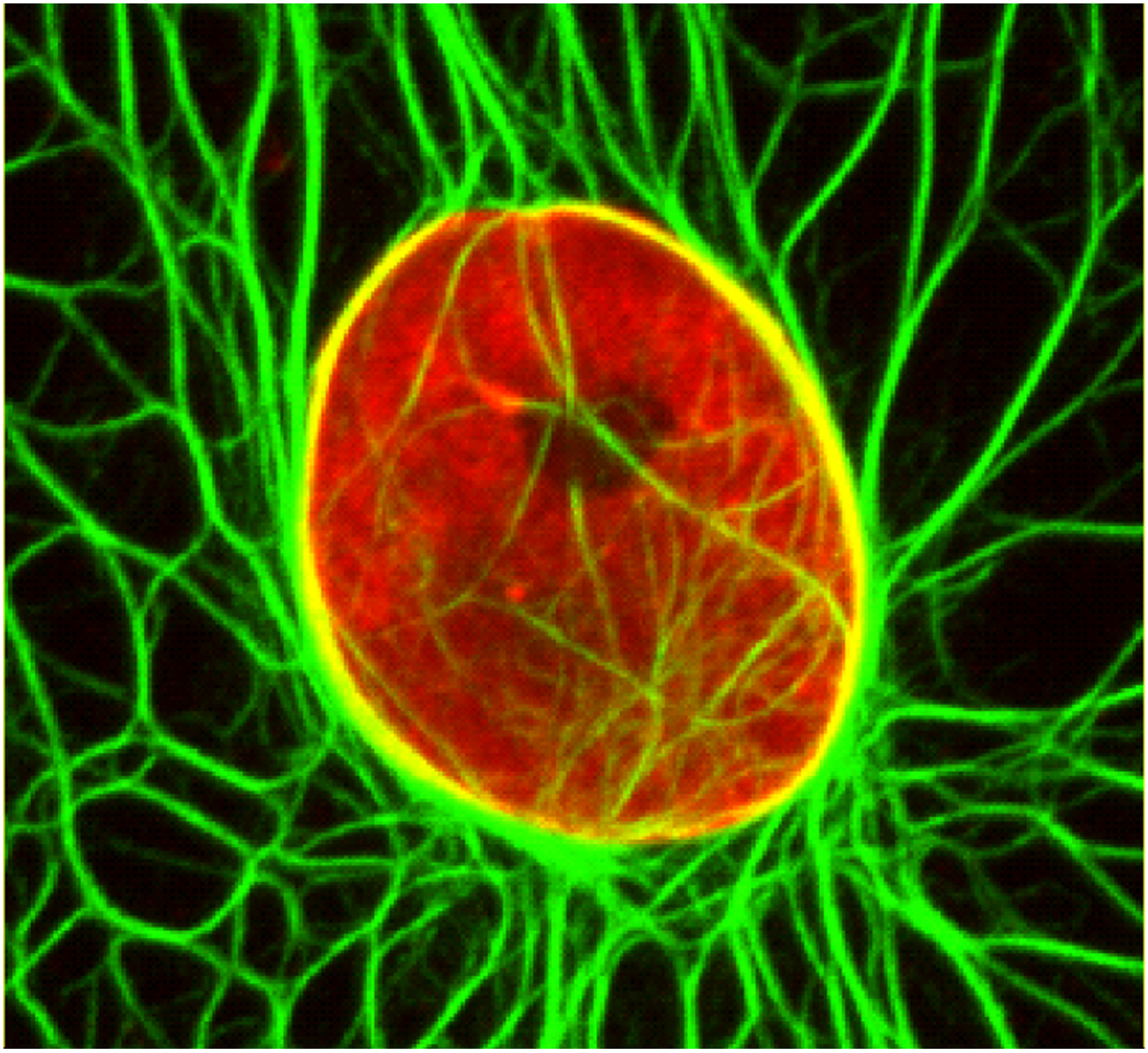

Figure 2.
Keratin-containing tonofibrils are distributed throughout the cytoplasm and surround, and are perhaps attached to the NE of a PtK2 rat kangaroo epithelial cell. This cell, expressing GFP-Keratin 18 (green), was fixed and immunostained with lamin A/C (red) antibody. Figure represents a projection of z-stack images obtained by confocal microscopy.

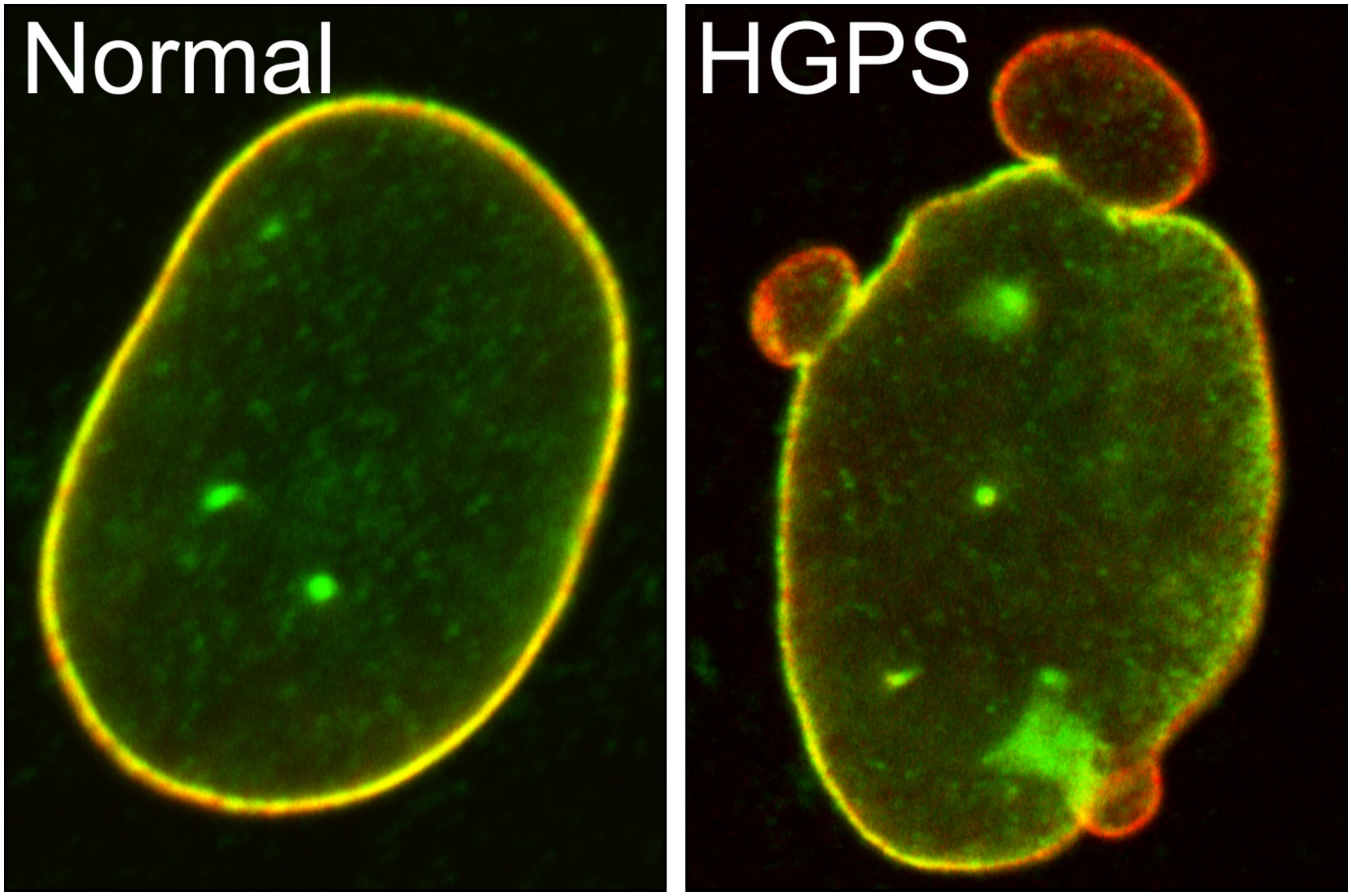

Figure 3.
The localization of lamins A/C and B1 in skin fibroblasts taken from a normal individual (left) and a patient with the HGPS mutation (G608G) in *LMNA* (right). These cells were fixed and immunostained with antibodies against lamin A/C (red) and lamin B1 (green). Note the separation of the A and B-type lamins in the blebbed regions.

Table 1

Mutations in genes encoding NE proteins known to cause diseases collectively known as the nuclear envelopathies/laminopathies.

Protein with mutations	Disease	Nuclear Shape	Reference
Lamins			
Lamin A/C	Autosomal dominant and recessive Emery-Dreifuss muscular dystrophy (AD-EDMD, AR- EDMD)	Honeycomb lamina	[27]
Lamin A/C	Limb-girdle muscular dystrophy type 1B (LGMD1B)	Blebbed	[28,29]
Lamin A/C	Dilated cardiomyopathy with conduction defect disease (DCM-CD)	Blebbed	[27]
Lamin A/C	Familial partial lipodystrophy of the Dunnigan type (FPLD)	Honeycomb lamina, Blebbed	[27,30]
Lamin A/C	Lipoatrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy, and leukomelanodermic papules (LDHCP)	Blebbed	[31]
Lamin A/C	Mandibuloacral dysplasia with type A lipodystrophy (MADA)	Honeycomb lamina, Blebbed	[32]
Lamin A/C	Charcot-Marie-Tooth disease type 2B1 (CMT2B1)	N/A	[33]
Lamin A/C	Hutchinson-Gilford progeria syndrome (HGPS) and atypical progeria syndrome	Blebbed, lobulated	[34••, 35,36]
Lamin A/C	Atypical Werner syndrome	blebbed	[37]
Lamin B1 (tandem gene duplication)	Autosomal dominant leukodystrophy (AD-LD)	Normal, distorted NE	[38]
Lamin B2	Barraquer-Simons syndrome (BSS)	N/A	[39]
LNM proteins			
Emerin	X-linked Emery-Dreifuss muscular dystrophy (XL-EDMD)	Honeycomb lamina, Blebbed, distorted NE	[40,41]
MAN1	Buschke-Ollendorff syndrome (BOS), melorheostosis	N/A	[42]
Lamin B receptor (LBR)	Greenberg dysplasia	Hypolobulated	[43]
Lamin B receptor (LBR)	Pelger-Huet anomaly (PHA)	Ovoid (lobulated for normal nuclei)	[44]
ONM proteins and the associated protein			
Nesprin-1	Arthrogryposis multiplex congenita (AMC)	Normal in human, elongated in mice	[45–47]
Nesprin-1	Dilated cardiomyopathy (DCM)	Normal	[47]
TorsinA	Torsion dystonia	Normal, distorted NE	[48]
Nucleoporins and the associated protein.			
Nup155	Atrial fibrillation and early sudden cardiac death	N/A	[49]
Nup62	Autosomal recessive infantile bilateral striatal necrosis (IBSN)	N/A	[50]
Ran binding protein 2 (RanBP2)	Acute necrotizing encephalopathy (ANE)	N/A	[51]
ALADIN	Achalasia-Addisonianism-Alacrimia syndrome (AAA)	Normal	[52]
Others			
Zinc metalloprotease STE24 homolog (Zmpste24)	HGPS, mandibuloacral dysplasia (MAD) and restrictive dermopathy (RD)	Blebbed	[53]
Zinc metalloprotease STE24 homolog (Zmpste24)	Autosomal recessive restrictive dermopathy (AR-RD)	Blebbed	[54]

Protein with mutations	Disease	Nuclear Shape	Reference
Lamina-associated polypeptide 2α (LAP2α)	Dilated cardiomyopathy (DCM)	Normal	[55]