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REVIEW

Interplay of the nuclear envelope with chromatin in physiology and pathology

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ABSTRACT

The nuclear envelope compartmentalizes chromatin in eukaryotic cells. The main nuclear envelope components are lamins that associate with a panoply of factors, including the LEM domain proteins. The nuclear envelope of mammalian cells opens up during cell division. It is reassembled and associated with chromatin at the end of mitosis when telomeres tether to the nuclear periphery. Lamins, LEM domain proteins, and DNA binding factors, as BAF, contribute to the reorganization of chromatin. In this context, an emerging role is that of the ESCRT complex, a machinery operating in multiple membrane assembly pathways, including nuclear envelope reformation. Research in this area is unraveling how, mechanistically, ESCRTs link to nuclear envelope associated factors as LEM domain proteins. Importantly, ESCRTs work also during interphase for repairing nuclear envelope ruptures. Altogether the advances in this field are giving new clues for the interpretation of diseases implicating nuclear envelope fragility, as laminopathies and cancer.

Abbreviations: na, not analyzed; ko, knockout; kd, knockdown; NE, nuclear envelope; LEM, LAP2-emerin-MAN1 (LEM)-domain containing proteins; LINC, linker of nucleoskeleton and cytoskeleton complexes; Cyt, cytoplasm; Chr, chromatin; MB, midbody; End, endosomes; Tel, telomeres; INM, inner nuclear membrane; NP, nucleoplasm; NPC, Nuclear Pore Complex; ER, Endoplasmic Reticulum; SPB, spindle pole body.

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Elements of the nuclear envelope

The nuclear envelope (NE) compartmentalizes chromatin in eukaryotic cells. It is composed of two phospholipid bilayers, the inner and outer membranes (INM and ONM), separated by a perinuclear space of approximately 30–50 nm [1–3]. The ONM is an extension of the endoplasmic reticulum (ER) and is directly connected with the INM at the nuclear pore sites [1,4] (Figure 1). Both the ONM and INM contain NE transmembrane proteins, synthesized in the ER, and successively distributed in the two compartments [4–6]. Below and interconnected with the INM, there is the nuclear lamina, which in mammalian cells includes A- and B-type lamins. Principal A-type lamins are lamin A and C, while the B-type are B1 and B2. The LMNA gene encodes the A-type lamins, whereas LMNB1 and LMNB2 genes encode lamins B1 and B2, respectively. The super-molecular organization of lamins into a meshwork interconnected with the INM has been dissected biochemically [7,8], and more recently detailed with refined technologies for imaging studies as 3D-SIM (structured illumination microscopy), PALM (photoactivated localization microscopy) and dSTORM (direct stochastic optical reconstruction microscopy) [9–12]. 3D-SIM delivers ~120 nm XY resolution images of mammalian cell nuclei [13]. This analysis showed that each of the lamins, A, C, B1, and B2, forms distinctive separate meshwork [9]. PALM and dSTORM, which allow scaling XY resolution to 20–100 nm, confirmed this meshwork organization [10,11,13,14]. Cryo-electron tomography has shown, besides, that A- and B-type lamins assemble into tetrameric filaments of 3.5 nm thickness [10]. Single molecule tracking has demonstrated the dynamic nature of lamins in the native cellular environment [12].

In situ cryo-electron microscopic imaging combined with biochemistry has provided, on the other

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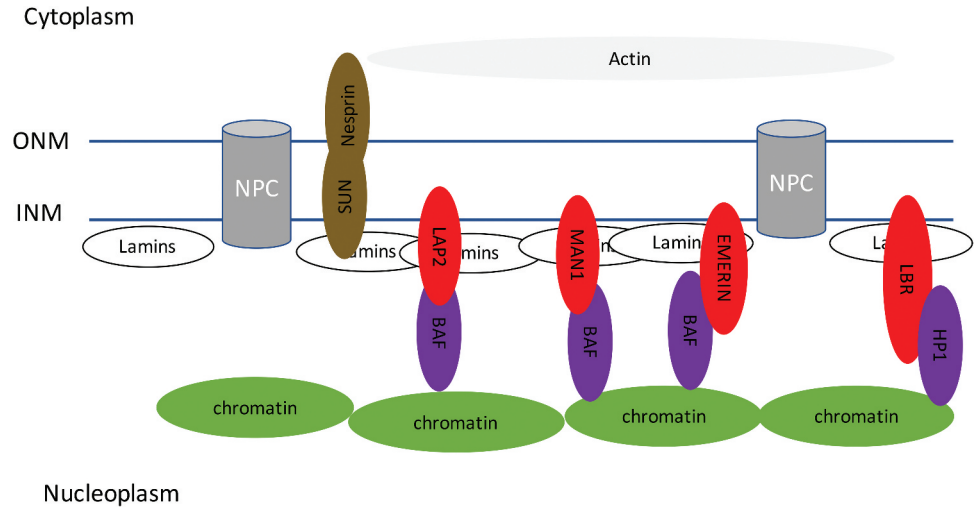

Figure 1. Schematic representation of the NE and of its components. The NE is composed of two phospholipid bilayers (INM and ONM), separated by a perinuclear space. The ONM is an extension of the ER and is directly connected with the INM at NPCs. Both the ONM and INM contain a set of proteins, including the LEM domain proteins, as LAP2, emerin, and MAN1. The LINC complex puts in contact the lumen of the NE with the cytoskeleton and is formed by the SUN and KASH proteins as nesprin. Chromatin is at the nuclear periphery via bridging elements as BAF.

end, the pseudo-atomic dissection of the nuclear pore complexes (NPCs) [15]. These are megadalton proteinaceous channels composed of more than 30 different nucleoporins [16]. NPCs allow import and export and diffusion of proteins, RNAs, and ions between the nucleus and the cytoplasm [15].

The INM hosts a set of proteins, including the LEM domain proteins, as LAP, emerin, and MAN1 [4,17,18]. The LINC complex puts in contact the lumen of the NE with the cytoskeleton. This complex is formed by the SUN and KASH proteins, which cross the ONM and the INM [19]. SUN (Sad1, Unc-84) domain proteins are associated with the INM, and KASH (Klarsicht, ANC- 1, Syne Homology) domain proteins reside in the ONM [19]. There are at least six SUN domain proteins in humans, SUN1 and SUN2 are the best characterized [20], while KASH domain proteins include nesprins 1 and 2 in mammals, which bind F-actin [21].

Altogether the different elements of the NE are implicated in nuclear properties, including chromatin organization and function.

Association of chromatin with the nuclear envelope

A spatially defined organization of chromatin that includes the association of specific domains with the nuclear periphery was historically hypothesized by Carl Rabl and Theodor Boveri [22] and successively observed by in situ hybridization by Cremer and Cremer in 2010 [23]. The genome-wide characteristics of the spatial architecture of chromatin were dissected successively by chromatin conformation capture (3 C)-based techniques. These studies identified topologically associating domains (TADs) [24] and chromatin domains linked with the lamina (LADs) [25]. In human cells, LADs are ~1,000 to 1,500. They possess features of heterochromatin [25] and are transcribed and replicated depending on their attachment status to the lamina [26]. Lamins also associate with euchromatic regions, in the nucleoplasm [27]. This association involves A-type lamins, while B-type lamins link the heterochromatin [27].

The NE associates with the chromatin via multiple factors. LEM domain proteins as LAP2ß, MAN1, and emerin bridge with the chromatin via BAF [28–30]. LBR, on the other hand, establishes contacts with heterochromatin via HP1 [30,31] (Figure 1). In accordance with the concept that the organization of the chromatin intertwines with the NE, modifications of lamins and NE factors cause its redistribution. The mutation of LBR and A-type lamins, for example, produces the relocalization of heterochromatin from the

periphery to the nuclear interior. This phenotype recalls the one of mouse retinal rod cells, which lack both A-type lamins and LBR [30].

Centromeres and telomeres play a relevant role in the organization of the chromatin at the NE. Carl Rabl first described a nonrandom organization of centromeres often associated with the NE [22]. This so-called Rabl configuration was observed in salamander larvae and successively found in other organisms, including yeast, where centromeres are clustered and attached to the NE [32]. In Saccharomyces pombe, centromere attachment to the NE depends on the centromere-bound protein Csi1 that bridges the centromeres through interactions with the SUN domain protein Sad1 [33]. Disruption in this interaction causes chromosome missegregation [33,34]. Julie Cooper and coworkers extensively studied the bouquet of telomeres and centromeres at the NE [35], demonstrating that the association of centromeres with the LINC complex controls spindle assembly in fission yeast [34]. These studies also point to the functional redundancy between centromeres and telomeres in enabling the formation of the meiotic spindles [36]. In addition to chromosome segregation, centromere tethering at the NE mediates peri-centromeric heterochromatin and subsequent gene silencing, through molecular association with Lem2 as shown in fission yeast [37]. The advent of 3 C-based technologies showed that this attachment to the NE limits topological entanglement of the budding yeast genome and facilitates chromosome segregation [38]. Importantly, recent evidence shows that centromeres influence genome organization and chromosome architecture, especially in yeast [39]. Advanced centromere labeling and 3D superresolution have demonstrated that alterations of human centromeres cause an apparent increase in the chromatin volume occupied with alpha-satellites in cancer cells [40,41]. Yet, in human cells, centromeres are not typically located at the periphery, except for specific cell types such as neutrophils where they are often associated with the NE [42]. Nonetheless, similar to finding in yeast, distribution at the NE and movements of mouse and human centromeres are required to form a chromosome bouquet structure that promotes homologs pairing during meiosis [43]. However, this nonrandom positioning of repetitive sequences tends to be transient, occurring just before or during meiotic recombination, potentially to enable the synaptonemal complex formation and shuffling of maternal and paternal genetic material through recombination.

Telomere tethering at the NE has been described in yeast and dissected in mammalian cells in meiosis [36,44–46]. In meiotic cells, the nuclear periphery organizes telomeres into the bouquet at the centrosomal pole of the nucleus to facilitate homolog pairing. This process is mediated by cytoplasmic dynein, SUN1, and KASH5, in the ONM [47]. SUN1 associates with telomeres at the INM, while KASH5 mediates dynein connection at the ONM.

Although the full picture is not yet defined, in mammalian somatic cells too, there is evidence that the NE affects the intra-nuclear topology and dynamics of telomeres [48,49], along with their homeostasis and epigenetics [50]. A-type lamins contribute to repair dysfunctional telomeres by stabilizing 53BP1 protein levels [51]. Advanced time-lapse imaging has shown the connection between DNA repair occurring at uncapped telomeres, and the proteins 53BP1 and SUN1 and SUN2, along with microtubules [52]. The nuclear factor LAP2α interacts with telomeres and lamin C in telophase, and with nucleoplasmic lamin A/C foci and with the lamina in interphase [53]. Lamins also interconnect with interstitial telomere sequences via the telomeric factor TRF2 [54]. This link could be critical for the formation of chromosome loops between telomeres and interstitial telomeric sequences [54].

Dynamics of chromatin and nuclear envelope in open mitosis

When higher eukaryotes enter mitosis, the nucleus opens up to let chromosome association with the spindle microtubule arrays and segregation into daughter nuclei [55]. A post-translational phosphorylation scheme of NE components triggered at the onset of mitosis controls NE disassembly [56]. The kinases involved in NE dismantling include cyclin-dependent kinase 1, Aurora kinases, Polo-like kinase 1, and Never in mitosis kinase [56]. NE disassembly also involves phosphatases,

namely protein phosphatase 1 and protein phosphatase 2A [56].

The process of NE disassembly requires the phosphorylation of nucleoporins in NPCs [57,58], and the phosphorylation of NE associated factors that induces their dissociation from lamins and chromatin. If this dissociation process does not occur, proper segregation of chromosomes is impaired [59]. The mitotic phosphorylation of the protein BAF reduces its affinity for chromatin, which contributes to NE disassembly [60]. Upon NE breakdown and NPC disassembly, INM and ONM elements go into the ER or the cytoplasm [61]. At this stage, cells enter prometaphase, mitotic spindle assemblies, chromosomes are organized at the metaphase plate and successively separated during anaphase [62]. At late anaphase, the NE starts to be reformed by ER fragment assembly and membrane resealing to recreate the compartmentalization between the nucleus and the cytoplasm [63,64]. The inactivation of the cyclin-dependent kinases and dephosphorylation of proteins as BAF allows recreating the connection of the NE with chromatin [65]. The compact structure of anaphase chromosomes favors the correct reorganization of the NE by preventing an invasion of membranes into chromatin [55].

In human cells, it is during the postmitotic phase of nuclear reassembly that telomeres enrich at the NE via an interaction between SUN1 and the telomeric protein RAP1 [49] (Figure 2). Telomere tethering at the nuclear rim drives chromatin domain reorganization, which at the steady-state includes the juxtaposition of heterochromatin at the nuclear lamina and LAD distribution [49]. At the end of telophase, NE reassembles and includes NPCs. NPC inclusion in the NE may happen either via the insertion of immature pre-NPCs or by direct assembly of the complexes at the NE [66].

During NE formation the endosomal sorting complex required for transport (ESCRT) ensures the continuity of the nuclear membrane [67,68] (Figures 2 and 3). The ESCRT machinery includes three protein families, the ESCRT I, II, and III. ESCRTs play a role in also in endosome trafficking [69,70] and in cell division [71,72], and a striking conceptual aspect is that they use common elements in the different pathways [73]. At the NE, the ESCRT CHMP4B recruits CHMP2A. CHMP4B is brought into the complex by the ESCRT CHMP7 and by UFD1 [74]. CCD21B, VPS4 and Spastin participate to ESCRT activity at the NE by regulating the spatio-temporal distribution of the macro-complexes and finalizing the membrane sealing process [73,75]. The ESCRT associated factor ALIX contributes to INM properties [76].

Mechanistically, CHMP7 acts as a membrane-binding module; it interacts with the ER and

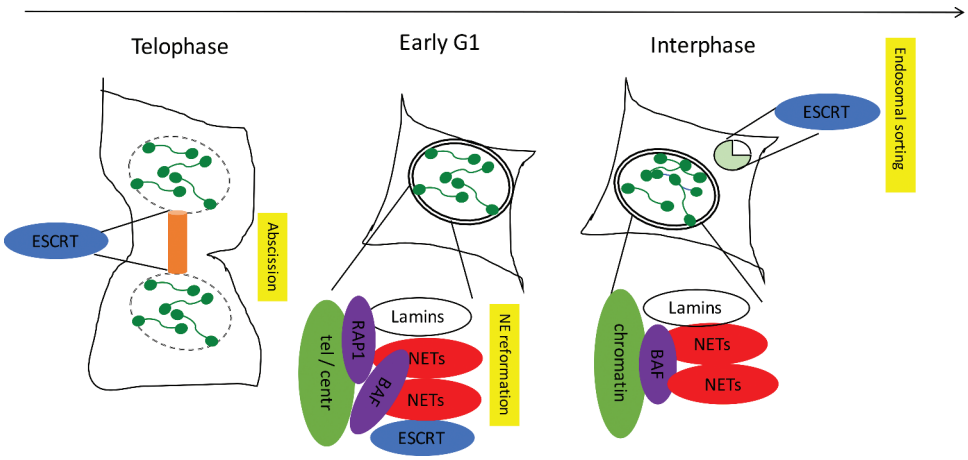

Figure 2. ESCRTs act in multiple cellular pathways including NE assembly. The ESCRT machinery works in telophase to contribute to the abscission process at the microtubule-rich structure known as the midbody (in orange). In early G1, ESCRTs participate to NE reformation. Here, ESCRTs, lamins, NE transmembrane proteins, and chromatin-associated factors work together determining spatial reorganization of chromatin. In interphase, ESCRTs play a pivotal function in endosomal trafficking. NETs, NE transmembrane proteins.

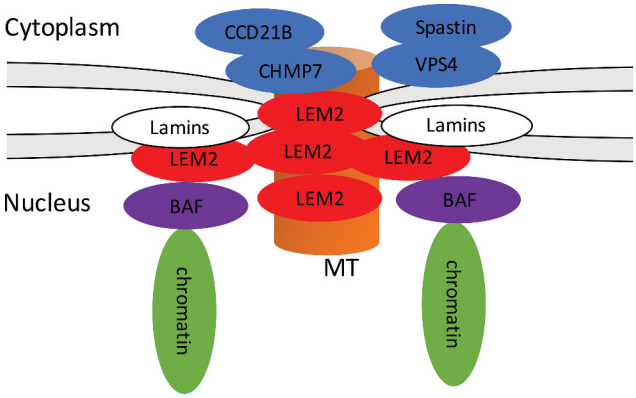

Figure 3. LEM2 condensation at the NE mechanistically links the ESCRT machinery to NE reassembly. A sealing process finalizes NE reassembly at the end of mitosis. This process starts with the condensation of the lamin associated factor LEM2 on mitotic spindle residual microtubules fibers (in orange). LEM2 condensation activates ESCRTs (in blue) that disassemble microtubules and allow membrane sealing. LEM2 binds BAF, associating chromatin to the macromolecular complex. MT, microtubules.

provides a platform to direct NE recruitment of ESCRT factors [74]. The INM LEM family member LEM2 (Lem2p in yeast) works with CHMP7 in fission yeast and human cells [77]. The recruitment at the NE of ESCRTs depends on LEM2. LEM2 enriches with CHMP7 at the same regions of the chromatin disk periphery. In yeast, it has been shown that telomere maintenance depends on ESCRT activity [78]. A new set of data implicates liquid-liquid phase separation of LEM2 in the polymerization of ESCRT CHMP7 around residual spindle microtubule bundles (Figure 3). These phase separation studies give a dynamic molecular picture bridging LEMs, ESCRTs, and the chromatin binding factor BAF [79].

Nuclear envelope defects and chromatin dysfunction in disease

Defects of the NE coupled with chromatin dysfunction characterize a panoply of human diseases. The fact that elements of the NE and chromatin are intimately linked is supported by the knowledge that mutations of diverse factors impinging on the NE as LEM domain proteins, ESCRTs or lamins, converge into common disease phenotypes of chromatin disorganization and dysfunction (Table 1 and Figure 4).

A paradigmatic example of NE disease associated with chromatin dysfunction is the Hutchinson Gilford Progeria Syndrome (HGPS). HGPS is a rare genetic disease due to a de novo C ≤ T transition in the LMNA gene that exposes a cryptic splice site, which generates the permanently farnesylated Δ50 variant of lamin A, known as progerin [80,81]. Although the full understanding of the in vivo pathological pathways that eventually lead to the HGPS clinical pattern is still under investigation, some aspects of the disease have been clarified. Importantly, as in other genetic diseases, the HGPS mutation impinges on mesenchymal stem cell properties [82,83] and causes autocrine and paracrine dysfunction of cells and tissues [84]. At the nuclear level, the expression of progerin causes dysmorphism, abnormal intra-nuclear chromatin distribution, DNA damage, and telomere attrition [85–89]. The HGPS mutation creates new associations as compared to wild type lamin A, abolishes existing interactions, or causes the delocalization or dysfunction of lamin A partners. Loss of lamin A interaction with 53BP1, for example, appears to account for the DNA repair defects observed in lamin mutants [90]. The chromatin defects found in HGPS patient cells likely reflect the association of lamins with the NURD chromatin remodeling complex [91]. Loss of another lamin interacting-protein, the Suv39h1 methyltransferase, improves DNA repair and extends the lifespan of a progeroid mouse model with impaired prelamin A maturation, suggesting that HGPS causes Suv39h1-mediated epigenetic alterations in the chromatin [92]. A-type lamin interaction with the telomeric factor TRF2 and the association of the LAP2α with telomeres provide evidence for the role of A-type lamins and progerin in telomere homeostasis [54]. Intriguingly, while the complete picture of centromere positioning at the NE remains elusive, data show that the HGPS LMNA mutation disrupts the peripheral clustering of centromeres in dermal fibroblasts from affected patients [93].

A further element fueling the concept that NE fragility and chromatin are interlinked in pathology derives from two paradigmatic papers on ESCRT proteins [68,147]. These studies have shown how ESCRT CHMP7 contributes not only to NE

Table 1. Defects of NE elements converge into common disease phenotypes. In line with the interplay between the NE and chromatin organization and function, mutations of NE components or associated factors converge into common phenotypes linked with chromatin.

Protein	Class	Compartment	Mutation	Organism	NE defect	Chromatin defect	Telomere defect	Mechanical defect	REFs
A-type lamins	intermediate filament	NE	LMNA ko	*H. sapiens*	yes	reorganization	localization, length, aberrations	reduced stiffness	[94,95,151]
			LMNA ko	*M. musculus*	yes	protrusions	localization, length, aberrations	increased deformability	[94,96]
			LMNA kd	*H. sapiens*	no	reorganization, positioning	length	high NE plasticity	[97–99]
			HGPS	*H. sapiens*	yes	reorganization, positioning	aberrations, length	increased stiffness	[99–102]
B-type amins	intermediate filament	NE	LMNB1/2 ko	*M. musculus*	yes	positioning	na	reduced deformability	[103,104]
			LMNB1/2 RNAi	*H. sapiens*		reorganization, positioning	na	na	[105]
			LMNB1 o/e	*H. sapiens*	yes	reorganization, positioning	no	increased stiffness	[103,106–108]
LBR	ERG4/ERG24	NE	LBR o/e	*H. sapiens*	yes	reorganization	na	na	[109]
EMERIN	LEM	NE	EMD ko	*M. musculus*	yes	reorganization, positioning	na	mechanosensitive genes deregulation	[110–112]
MAN1	LEM	NE	ΔMan1	*S. pombe*	no	no	localization	na	[110,113,114]
			RNAi	*H. sapiens*	yes	na	na	na	[110,113,114]
LAP2	LEM	NE, Chr, NP	ΔLap2	*S. pombe*	yes	na	localization	na	[53,110,113]
			RNAi	*H. sapiens*	yes	na	na	na	[53,110,113]
LAP1	Type II integral INM	NE	LAP1 ko	*M. musculus*	yes	na	na	na	[115]
			null LAP1A, C	*H. sapiens*	yes	na	na	reduced cellular motility	[115,116]
			null LAP1B	*H. sapiens*	yes	na	na	reduced cellular motility	[115,116]
NESPRIN/ SYNE	LINC	NE	DN-SYNE	*M. musculus*	yes	reorganization	na	intracellular force transmission	[117]
			null SYNE/SYNE RNAi	*H. sapiens*	yes	yes	na	intracellular force transmission	[118]
Sad1/UNC84 (SUN1/2)	LINC	NE	DN-SUN1	*M. musculus*	yes	reorganization	localization	intracellular force transmission	[46,49,117,119–121]
			null SUN1	*H. sapiens*	yes	reorganization	localization	intracellular force transmission	[46,49,117,119–121]
NUPs	Nucleoporins	NE, NPC	NUPs ko	*S. pombe*	yes	gene expression	na	ma	[122–124]
			Δmlp1, Δmlp2/nup1-LexA nup116Δ	*S. cerevisiae*	yes	reorganization	localization	na	[125,126]
			RNAi	H. sapiens	na	reorganization	na	reduced cellular mobility	[122–124,126]
BAF	DNA binding	NE, Cyt, Chr	BAF ko	*C. elegans*	yes	reorganization	na	na	[60,127,128]
			BAF ko	*H. sapiens*	yes	na	na	na	[129,148]
			BAF p.Ala12Thr	*H. sapiens*	yes	reorganization	na	na	[100,128,130]
AKTIP	UEV	NE, MB, End	AKTIP RNAi	*H. sapiens*	yes	reorganization	aberrations	na	[108,131,132,163–166]
			Ft1 kd	*M. musculus*	na	na	aberrations	na	[108,131,132,163–166]
Spastin	AAA ATPase	NE, MB, End	Spastin RNAi	*H. sapiens*	yes	na	na	na	[73,133–135]
Cmp7/ CHMP7	non-canonical ESCRTIII-like	NE, ER	cmp7Δ	*S. pombe*	yes	na	na	na	[136]
			RNAi	*H. sapiens*	yes	na	na	na	[137]

(*Continued*)

Table 1. (Continued).

Protein	Class	Compartment	Mutation	Organism	NE defect	Chromatin defect	Telomere defect	Mechanical defect	REFs
Vps32/ CHMP4B	ESCRT III	NE, MB, End	CHMP4B-GFP	*S. pombe*	na	na	na	defects in NE resealing in migrating cells	[73,137–140,151]
			CHMP4B-D129V	*H. sapiens*	yes	clearance of chromatin from intercellular bridge	na	na	[73,137–140,151]
Did4/ CHMP2A/B	ESCRT III	NE, MB, End	Did4 ko	*S. pombe*	yes	positioning	length	na	[67,73,137]
			CHMP2A/B ko	*H. sapiens*	yes	na	na	na	[67,73,137]
Vps4/ VPS4A/B	AAA ATPase	NE, MB, End	Vps4 RNAi	*S. pombe, S. japonicus*	yes	na	length	na	[71,73,137,138,141]
Lem2/LEM2	LEM	NE, ER, SPB	lem2Δ	*S. pombe*	yes	reorganization, positioning	localization	na	[37,77,113,142,143]
			LEM2 RNAi	*H. sapiens*	na	na	na	na	[37,77,113,142,143]
RAP1	Shelterin	Tel, Chr	Rap1 ko	*M. musculus*	na	na	aberrations	na	[49,144–146]

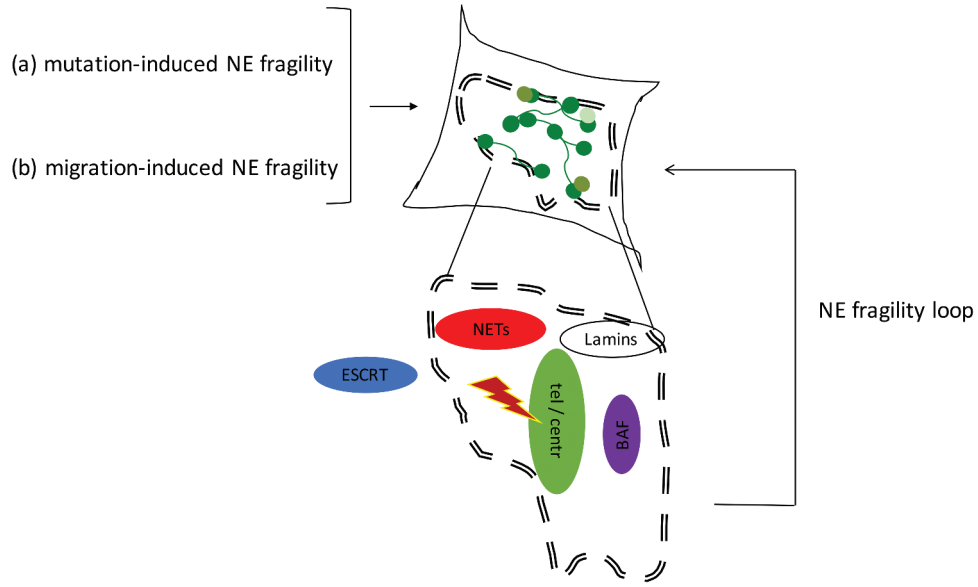

Figure 4. Disease-induced fragility of the NE Genetic diseases caused by mutations of ESCRTs or NE components (a), as HGPS, are characterized by NERDI and by the disorganization of macro-complexes needed for NE repair and reassembly. Therefore, cells from patients with HGPS (or with other similar diseases) are subject to a negative NE fragility loop. This trait is characteristic of cancer too, and further exasperated during metastatic invasion (b) by the exogenous mechanical pressure generated on the NE by cell migration in confined spaces.

reassembly in the final stages of cytokinesis but also to repair NE rupture during interphase (NERDI) [68,147]. Mechanistically, the repair sequence of NERDI involves a predominantly non-phosphorylated cytoplasmic population of BAF, that binds DNA and concentrates at nuclear ruptures, where it recruits LEM-domain proteins, driving the assembly of the ESCRT complex [148]. In HGPS cells, NERDI is observed and associates with ESCRT expression [149–151].

Cancer is a second example in which defects of the NE are coupled with chromatin dysfunction and linked to the disease phenotype [152,153]. Nuclear deformation and chromatin alterations are in fact in use for diagnosis and tumor classification since many years [154]. The evolution of imaging and computer science has then brought to next-generation cancer nucleotyping based on parametric machine-learning techniques that use quantitative data, as nuclear size, shape, and chromatin organization for classifying histopathology images. This approach, in its most recent interpretation, is based on nonparametric methods, including deep learning and digital performance optimization [155].

The cause-effect sequence of NE fragility in cancer is intricate since tumors are at the same time associated with mutations in lamin expression, with chromatin alterations and with extranuclear and extracellular mechanical impingements that converge into a NERDI phenotype [152–155]. NERDI exposes chromatin to nucleases, creates further genome instability [152], including the formation of micronuclei [156]. Elements that are part of the NE, or associated with it, are implicated in this phenotype. BAF, for instance, has been recently demonstrated to contribute to the repair of the NE by recruiting lamins and lamin-interacting factors [157]. The reduction of ESCRTs contributes to NE fragility and tumorigenesis [68] and impinges on the intrinsic properties of micronuclei [158].

Telomere association with the NE can be part of a NE fragility loop contributing to cancer aggressiveness. Cell over-replication causes telomere crisis, dicentric chromosomes, chromatin bridges, that produces NE defects, which, in turn, can generate further telomere dysfunction [159–161].

Along with this, NE fragility in cancer is further exasperated during metastatic invasion by the exogenous mechanical pressure generated on the NE by cell migration in confined spaces [147]. By this line of reasoning, the depletion of AKTIP, a factor associated with the NE and with telomeres,

produces nuclear alterations, telomere fragility, and cancer aggressiveness [162–166].

Given all these data together, drugs that can act in NE assembly, targeting BAF or LEM containing factors [167], along with ESCRTs, could be investigated for their ability to rescue cell homeostasis in laminopathies and cancer.

Concluding remarks

Physical proximity of the NE to chromatin, along with the importance of the NE in separating and protecting the chromatin from the cytoplasm, make it logical to presume an intimate interplay between chromatin and the NE. The physical nonrandom proximity of portions of chromatin to the nuclear periphery was observed more than a century ago [22]. The molecular dissection of the elements contributing to these interactions has been an ongoing field of research, identifying, for example, the positioning of telomeres and centromeres at the NE [22,32,48–50]. The area has had an acceleration in the resolution-revolution era. Imaging and 3 C-based technology have delivered the picture of single-molecule super-organization, as for lamin meshworks, and for intramolecular interactions, as in TADs [24] and LADs [25]. The possibility of observing the dynamics of postmitotic NE assembly around chromatin have contributed to a new vision of cell biology, namely a seamless succession of processes that are intertwined, rather than a stepwise sequence of independent events. These high-resolution techniques have also been instrumental for the dissection of a new and particularly exciting area of study focusing on NERDI and thereof players, as the ESCRT CHMP7 [68,74,147]. This field, in particular, is in rapid evolution. Many questions are open, as the full characterization of the ESCRT complex at the NE, and the dissection of the elements involved in the interplay between NE reorganization and the dynamics of chromatin assembly, but this field has given new or revised suggestions for experimental medicine.

Disclosure of potential conflict of interest

No potential conflict of interest was reported by the authors.

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