Review

The Biology of the Nuclear Envelope and Its Implications in Cancer Biology

Maria Alvarado-Kristensson 1,2 and Catalina Ana Rosselló 2,3,*

1 Molecular Pathology, Department of Translational Medicine, Lund University, Skåne University Hospital, 20502 Malmö, Sweden; maria.alvarado-kristensson@med.lu.se
2 Laboratory of Molecular Cell Biomedicine, University of the Balearic Islands, 07121 Palma de Mallorca, Spain
3 Lipopharma Therapeutics, Isaac Newton, 07121 Palma de Mallorca, Spain
* Correspondence: ca.rossello@uib.es or ca.rossello@lipopharma.com; Tel.: +34-971-173-331

Received: 23 March 2019; Accepted: 25 May 2019; Published: 27 May 2019

Abstract: The formation of the nuclear envelope and the subsequent compartmentalization of the genome is a defining feature of eukaryotes. Traditionally, the nuclear envelope was purely viewed as a physical barrier to preserve genetic material in eukaryotic cells. However, in the last few decades, it has been revealed to be a critical cellular component in controlling gene expression and has been implicated in several human diseases. In cancer, the relevance of the cell nucleus was first reported in the mid-1800s when an altered nuclear morphology was observed in tumor cells. This review aims to give a current and comprehensive view of the role of the nuclear envelope on cancer first by recapitulating the changes of the nuclear envelope during cell division, second, by reviewing the role of the nuclear envelope in cell cycle regulation, signaling, and the regulation of the genome, and finally, by addressing the nuclear envelope link to cell migration and metastasis and its use in cancer prognosis.

Keywords: nucleus; envelope; γ-tubulin; mitosis; cell cycle; signaling; genome; cancer; diagnosis; metastasis

1. Introduction

Papanicolaou’s smear test [1] is a routine check for uterine and cervical cancer. In addition, it has been implemented for a variety of specimens, such as fine needle aspiration biopsies, cerebrospinal fluid, pleural fluid, and urine samples, among others [2,3]. This cancer diagnosis test is based on a combination of changes in the staining, size, and shape of the nuclear chromatin. The eukaryotic nucleus encloses and regulates this chromatin by using a double membrane (nuclear envelope, NE), which, in turn, provides a unique molecular and biochemical environmental protective mechanism against potentially damaging cytoplasmic enzymatic activities, such as oxidative metabolism.

NE includes three interconnected domains with morphological differences: The inner nuclear membrane (INM) and outer nuclear membrane (ONM) and the pore membranes. These two individual lipid bilayers are separated by a luminal space of 30–50 nm in human cells, named the lumen or perinuclear space. For the transport of macromolecules in and out of the nucleus, both NM connect to form pore membranes where the nuclear pore complexes (NPCs) responsible for transport regulation are inserted [4–6]. Indeed, INM and ONM form discrete domains of a single membrane system separated by the NPCs [4,5]. The ONM is contiguous with the rough endoplasmic reticulum (ER) and contains ribosomes on its outer surface [4,5]. Furthermore, the ONM is connected to the cytoskeleton through its integral proteins, and in turn, these proteins connect to the luminal parts of INM proteins at the luminal space, all in all connecting the cytoskeleton to the nucleoskeleton and chromatin. Although INM, ONM, pore membranes, and ER originate from a continuous structure, they maintain their identities to a large
extent through unique profiles of integral-membrane and other associated proteins, together with specific compositions of lipids and cholesterol [7–9]. In addition, the protein composition of the nuclear envelope membranes is variable across different mammalian tissues (reviewed in Reference [10]).

In metazoan organisms, the primary scaffold of NE is provided by a fibrous layer called the nuclear lamina. This thick protein layer that underlies the INM has been described in studies with isolated NEs, since nuclear lamina is resistant to most chemical extractions used in biology. The most abundant proteins of the nuclear lamina are, by far, three polypeptides of around 65–70 kDa that correspond to type V intermediate filament proteins and are named lamins [11,12]. It is estimated that there are roughly 3,000,000 copies of lamins in a typical mammalian nucleus [13]. The specific lamin nucleoskeleton is distinct from the nuclear matrix that supports chromatin inside the nucleus. Four lamin proteins are expressed in mammalian somatic cells. A-type lamins (lamins A and C) are produced by alternative mRNA splicing of \( \text{LMNA} \) gene, whereas B-type lamins (lamin B1 and B2) are encoded, respectively, by \( \text{LMNB1} \) and \( \text{LMNB2} \) genes. Lamins C2 and B3 are germ-cell-specific isoforms produced by alternative splicing of \( \text{LMNA} \) and \( \text{LMNB1} \), respectively. B-type lamin expression occurs early in embryonic development and persists ubiquitously through adult life. In contrast, the A-type lamins are expressed in an asynchronous and developmentally regulated manner and are only detected after tissue differentiation (reviewed in [14]). Indeed, before day 10 of murine embryonic development, no A-type lamins are detected in the embryo proper [15,16]. The last constituent of the nuclear lamina is a collection of integral and associated proteins of the INM.

The gatekeeper function necessary for the translocation of proteins in and out of the nucleus is controlled principally by the NPC. The NPCs are large assemblies of >60 MDa in mammals. Several copies of a set of 30 diverse proteins, termed nucleoporins (NUPs), are found in these structures (reviewed in [6]). Only a restricted number of structural domains are found in the nucleoporins sequence. Those domains are transmembrane domains, Phe-Gly (FG) repeats, WD domains, α-helices, and β-propellers [17–19]. Around 2000–3000 NPC units are found in an average mammalian nucleus. FG-NUPs, in particular, play the most relevant role in defining the NPC diffusion limit and the list of nuclear transport receptors that might be shuttled through the NPC ([20] and reviewed in Ref. [21]). Indeed, NPCs are not a mere gateway to the nucleus. First, the size and maturation of nuclear pores is a crucial event to the nuclear import and nuclear growth and size at the end of mitosis [22,23], reviewed in Ref. [24] and during interphase [23,25,26], as shown in several vertebrate models. Second, NPCs might alter nuclear morphology through the physical link with lamins [27]. Third, nucleoporins are a model of long-term protein endurance: NPCs are sustained over the lifetime of a cell by means of a slow but finite interchange of its steadily more stable subcomplexes [28]. In tumorigenesis, the incidental finding of Nup88 as a biomarker of cancer [29,30] opened the door to detection of high levels of Nup88 in several types of tumors [30–36]. Beyond this protein, only a small number of nucleoporins have been associated with tumorigenesis. These include proteins Nup62, Nup88, Nup98, Nup214, and Nup358/RanBP2, all of them elements of the trafficking pathway and are specifically related to the export of mRNA (reviewed in Ref. [37]). In the literature, increases in the number of NPCs were related with more aggressive tumors [38–41].

In addition, nuclear envelope transmembrane (NET) proteins are also found both INM and ONM. This host of integral proteins might be tissue-specific for up to 60% of their protein elements [42]. Most NETs bind lamins and interact with chromatin (reviewed in [43]). The most known NET is emerin, which is encoded by the \( \text{EMD} \) gene in humans. Emerin is a founding member of the LEM domain-containing integral proteins of the inner nuclear membrane in vertebrates, where LEM is named for LAP2, emerin, and MAN1 (reviewed in [44]). Emerin is highly expressed in cardiac and skeletal muscle and several mutations affecting this gene cause X-linked recessive Emery–Dreifuss muscular dystrophy (EDMD).

More than preserving genetic material and providing architecture and mechanical support in eukaryotic cells, the NE is a key cellular hub that plays a dynamic role in the control of cell cycle regulation, mitosis, apoptosis, DNA repair, ageing, nuclear architecture, signaling, chromatin
organization, gene expression regulation, and cell migration [45–51]. All of these various functions are critical for the processes of tumorigenesis, tumor growth, and metastasis. All in all, it is reasonable that the diagnosis of cancer relies on morphologically distinctive alterations in the NE that are only recognizable by the eye of a well-trained pathologist.

2. The Nuclear Envelope in Cell Division

Cancer is the result of uncontrolled cell division. NE proteins can mostly affect the cell cycle in higher eukaryotes when the cells undergo open mitosis and the nucleus architecture is dismantled to allow the partitioning of the genetic material between the daughter cells. Indeed, the finding in mammalian cells of the depolymerization of lamin polymers upon hyperphosphorylation of lamin A at the onset of mitosis was the first clue in NE regulating cell division [52–55].

2.1. Nuclear Envelope Disassembly at the Onset of Cell Division

Phosphorylation of NE proteins and of their binding partners drives the coordinated disruption of NE interactions and structures at the beginning of mitosis. Together with lamins, several NPC proteins and NETs are also phosphorylated by mitotic kinases (gp210, LAP2β, and lamin B receptor –LBR), as shown in human, murine, or avian models [56–59]. In human and Caenorhabditis elegans cells, the same occurs with barrier-to-autointegration-factor (BAF), a chromatin binding partner of several NETs connecting chromatin to NE [60,61] (reviewed in [62]).

Disassembly of the NE needs close coordination with the generation of the bipolar mitotic spindle. In prophase, NPC-attached dynein motors assist in the separation of the centrosomes [63,64]. Disassembly of NPCs is not a straight reversal of the assembly steps (reviewed in [65,66]). In many cases, components of the NE and NPCs actively participate in mitotic events when released from their interphase organization [67]. At the G2/M cell cycle transition, two nucleoporins participate in tethering centrosomes to the NE [68,69]. During prophase, these interactions might help microtubules in their function for NE breakdown [70] and for moving of sister centrosomes to opposite sides of the nucleus [68,69,71]. At the end of prophase, the NPC is dismantled releasing elements with important regulatory functions during mitosis: NUP358 at kinetochore functioning [72–74], NUP88 and other nucleoporins interfering with microtubule dynamics to promote spindle assembly, NUP98 in regulating the adenomatous polyposis coli (APC) [67,75–77] (reviewed in [65]).

During mitosis in animal cells, remodeled nuclear membranes intermix in a large part with the tubulo-vesicular mitotic ER [78], while NE vesiculation also occurs [79–86]. Regarding the over 100 different NETs in any given cell, several of them go into a storage form and others exert critical functions, such as RanGTP, the transport receptor importin/karyopherin β, and RepoMan ([87], reviewed in Ref. [6,88,89]).

Several features of cancer cells, such as lagging chromosomes, aneuploidy, and polyploidy, might occur after a failed NE breakdown at the onset of mitosis and the subsequent blocking of spindle assembly.

2.2. Nuclear Assembly After Cell Division

2.2.1. Chromatin Enclosing, INM Protein Recruitment, and NPC Formation

During metazoan anaphase, chromosomes cluster compactly together in a disc-like configuration whose surface drives nuclear assembly. During early telophase, NE reassembly is initiated by changes at this chromatin surface (i.e., removal of mitotic histone marks by phosphatases) and the dephosphorylation-induced binding of NETs and their associated membranes to chromatin (reviewed in [78]).

Several mechanisms combine to recruit ONM and INM proteins, constituents of NPCs, and lamins. In metazoa, INM proteins are attracted both by both specific interactions and by the general affinity of many INM proteins for chromatin/DNA, for example, LBR binds heterochromatin protein 1 (HP1) [90,91] and histone H3 [92–94]. Importantly, NET and NPC binding to mitotic chromosomes in
early telophase seems to drive NE reassembly [95–99], implicating phenylalanine and glycine (FG)-rich nucleoporins and the AT-hook-domain containing protein, ELYS/Mel-28 (Figure 1). ELYS localizes not only to NPCs, but is also associated with chromosomal kinetochores during cell division. At the end of mitosis, ELYS recruits the NUP107-160 subcomplex, which is required for the correct segregation of mitotic chromosomes [100,101]. In addition, in NPC assembly and chromatin decondensation, lysine demethylase LSD1 is required [102], while the Repo-Man-promoted dephosphorylation of histone H3 seems indispensable for targeting importin-b to mitotic chromatin [103] (Figure 1).

Engulfment of recently separated sister chromatids by the NE occurs in an astonishingly short timeframe thanks to deposits of membrane fragments on the chromatin surface that trigger the enveloping process (reviewed in [78,104]). It is still a matter of debate whether ER moves toward chromatin in the way of membrane sheets or tubules (reviewed in [105]). Regardless of the case, defects in any of these mitotic functions could affect the quality of cell division and lead to aneuploidy, a common feature of tumors [106]. In the metazoan, NPC formation occurs in two different phases of the cell cycle and through different assembly mechanisms: Post-mitotic NPC assembly and interphase NPC formation [18,107–110]. Two models for post-mitotic NPC assembly have been proposed: The insertion model claims that NPCs are reassembled into an intact nuclear envelope, while the enclosure model proposes that NPC assembly starts before the NE encloses the chromatin (reviewed in [111–113]). In any case, post-mitotic NPC assembly happens in a step-wise manner and it is subjected to fine surveillance mechanisms (reviewed in [65]). NPC assembly begins in early anaphase with soluble NPC proteins (Nup107-160 scaffold) positioning on the chromatin, mediated by Elys/Mel28, before membrane reformation. Then, it might be followed by the recruitment of transmembrane nucleoporins (reviewed in [24,108,109]). In the case of NUP153, it might even participate in the biogenesis of the lamina [114].

Surveillance mechanisms ensure correct post-mitotic reformation of NPCs (reviewed in [65]) and the assembly of the basket-like feature is particularly necessary to complete cytokinesis in a timely manner [114]. Aurora kinase B links the basket-like feature with cytokinesis, and this is currently explored as a chemotherapeutic approach in clinical trials against cancer [115].

The number of NPCs formed during interphase doubles prior re-entry into mitosis (reviewed in [111]). However, little is known about NPC formation during interphase, although it is differentially regulated compared to post-mitotic NPC assembly. Interphase NPC formation is dependent upon cyclin-dependent kinase (CDK) activity, but not upon ELYS/Mel-28 [116,117]. Kinetochores and microtubules are also essential in NE reassembly, particularly, in the recruitment of BAF to the chromatin template [118]. Acetylated Lem4 (ANKLE2) participates in this process by promoting the dephosphorylation of BAF [96,97,119]. The binding of BAF to chromatin is indispensable for most of the integral-membrane LEM-domain containing proteins to connect to chromatin through their interaction with BAF itself [118,120,121]. A recent elegant report using human cells showed that the role of BAF in nuclear assembly depends upon its ability to link distant DNA sites [122]. Microtubule organizer γ-tubulin may play a noncanonical and distinct role in promoting NE assembly [123]. A local suppression of microtubules during nuclear formation, fulfilled by chromatin-bound microtubule regulators, is required in X. laevis for proper pronuclear assembly and regular morphology of the nucleus [124]. An association of microtubules with the nucleoporin ELYS/Mel-28 and the NE reassembling GTPase, Ran, has been described in X. laevis [125]. In both X. laevis and mammalian cells, a γ-tubulin boundary made of γ-strings is formed around chromatin during NE assembly, and this γ-tubulin boundary ensures the formation of the lamina around chromatin by recruiting of lamin B (Figure 1) [123]. The formation of fibrillar aggregates of γ-tubulin was further confirmed upon chaperonin containing TCP-1 (CCT) action in vitro [126]. Shaping the nucleus and achieving a regular distribution of NPCs has been shown to depend upon the γ-tubulin complex protein 3-interacting proteins in Arabidopsis thaliana [127]. Furthermore, in human cells, expression of a γ-tubulin mutant that lacks the DNA-binding domain forms chromatin-empty nuclear-like structures, demonstrating that a persistent interplay between the chromatin-associated and the cytosolic pools of γ-tubulin is required for proper NE assembly [123].
The finding that several NETs (NET5, NET6, and NET7) partially concentrate on or around the mitotic spindle (i.e., Tmem201, WFS1, Tmem214, and others) suggests that a persistent interplay between the chromatin surface (i.e., removal of mitotic histone marks by phosphatases) and dephosphorylation-induced binding of nuclear envelope transmembrane proteins (NETs) and their associated membranes to chromatin. Engagement of recently separated sister chromatids by the NE occurs via deposits of membrane fragments on the chromatin surface that trigger the enveloping process. The NE is reformed from endoplasmic reticulum (ER) membranes, which contact chromatin either as tubules or sheets. After membrane deposition, NPC assembly allows importation of the elements for nuclear lamina assembly. Microtubule organizer γ-tubulin plays a distinct role in promoting this NE formation by providing a γ-tubulin boundary indispensable for NE assembly. At the onset of mitosis, the lamina meshwork is disrupted, but the γ-tubulin boundary around the mitotic chromosomes is maintained. During mitosis, chromatin-associated γ-strings link the sister chromatids to the cytosolic γ-string pool. Finally, at anaphase/telophase, the γ-tubulin boundary composed of cytosolic and chromatin-associated γ-strings forms a supporting scaffold that assists the formation of the nuclear envelope.

During telophase, γ-tubulin bridges connect the cytosolic and the nuclear γ-tubulin pools ([123], reviewed in [128,129]). The LINC protein nesprins recruit centrosomal proteins and regulate the nucleation of microtubules from the NE in myotubes [130]. The INM protein Samp1 is in contact with both γ-tubulin and SUN1 [131]. At the beginning of mitosis, during the rupture of the NE to the spindle microtubules, Samp1 might recruit γ-tubulin from the fenestrated NE. In the spindle, γ-tubulin and Samp1 complex together with augmins would potentially assist in the nucleation of the microtubules. Not to scale.

Figure 1. A model for the role of nuclear γ-tubulin in chromatin enclosing, inner nuclear membrane (INM) protein recruitment, and nuclear pore complex (NPC) formation in nuclear disassembly and reassembly upon cell division. (a) Schematic representation of the nucleus and nuclear envelope (NE) during interphase and subsequent mitosis. Post-mitotic reassembly of the NE is initiated by changes at the chromatin surface (i.e., removal of mitotic histone marks by phosphatases) and dephosphorylation-induced binding of nuclear envelope transmembrane proteins (NETs) and their associated membranes to chromatin. Engagement of recently separated sister chromatids by the NE occurs via deposits of membrane fragments on the chromatin surface that trigger the enveloping process. The NE is reformed from endoplasmic reticulum (ER) membranes, which contact chromatin either as tubules or sheets. After membrane deposition, NPC assembly allows importation of the elements for nuclear lamina assembly. Microtubule organizer γ-tubulin plays a distinct role in promoting this NE formation by providing a γ-tubulin boundary indispensable for NE assembly. At the onset of mitosis, the lamina meshwork is disrupted, but the γ-tubulin boundary around the mitotic chromosomes is maintained. During mitosis, chromatin-associated γ-strings link the sister chromatids to the cytosolic γ-string pool. Finally, at anaphase/telophase, the γ-tubulin boundary composed of cytosolic and chromatin-associated γ-strings forms a supporting scaffold that assists the formation of the nuclear envelope. (b) Magnified boxed area of NE at interphase: During interphase, γ-tubulin bridges connect the cytosolic and the nuclear γ-tubulin pools ([123], reviewed in [128,129]). The LINC protein nesprins recruit centrosomal proteins and regulate the nucleation of microtubules from the NE in myotubes [130]. The INM protein Samp1 is in contact with both γ-tubulin and SUN1 [131]. At the beginning of mitosis, during the rupture of the NE to the spindle microtubules, Samp1 might recruit γ-tubulin from the fenestrated NE. In the spindle, γ-tubulin and Samp1 complex together with augmins would potentially assist in the nucleation of the microtubules. Not to scale.
The finding that several NETs (NET5/Samp1/Tmem201, WFS1, Tmem214, and otefin) partially concentrate on or around the mitotic spindle, and in the case of the latter, the centrosome during mitosis together with the tissue specificity of many of the NETs affecting the cell cycle, suggests that further implications of these proteins in mitosis might come in the future (reviewed in [14]).

2.2.2. Spatial Distribution of NE Elements

Chromatin discs involve different areas: the “inner core” (the central region of the disc that faces the midzone), the “outer core” (the central region that faces away), and the “non-core” region (the peripheral edge of the disc) [16,118,132,133].

In metazoan, INM proteins and membrane destined for the NE make initial contacts at the non-core region with the γ-tubulin boundary before spreading around and engulfing chromatin [123,134]. Telomeric regions of sister chromatids are bound with unique proteins essential to nuclear architecture, as is LAP2α [98,99]. Furthermore, in newly forming nuclei, telomerizes localize to the periphery of the nucleus, suggesting that these regions are involved in the initial seed of nuclear assembly [135].

The core region (inner and outer) is the target for ESCRT (endosomal sorting complexes required for transport) pathway proteins to recruit the microtubule severing factor spastin and seal annular gaps in the newly formed NE [136–139]. This core is initially deficient in NPC formation, but the process begins at this site soon after membrane closure [133].

The relevance of NPCs in anchoring interactions necessary for nuclear shape maintenance and structural integrity is illustrated, first, by interactions between nucleoporins NUP53, NUP88 and NUP153 and lamins [140–142], second, by the finding of polymorphic, lobular nuclear shapes after the depletions of these nucleoporins [140,143,144], and third, by SUN domain-containing protein 1 (SUN1) preferential location in the vicinity of NPCs [145].

All in all, defects in NE proteins might cause an inability to disassemble the NE at mitosis onset (generating partially maintained connections between NE fragments and chromatin) and to reassemble NE at the end of mitosis, blocking proper chromosome segregation and resulting in micronuclei and aneuploidy [106]. The wrapping of all chromosomes into a sole nucleus is thus essential for preserving the integrity of the genome and preventing the development of tumors.

3. The Nuclear Envelope in Cell Cycle Regulation and Signaling

3.1. Nuclear Envelope in Cell Cycle Regulation

Several elements of the NE (lamin A, lamin B, LAP2α, γ-tubulin, and emerin) have been shown to interfere with the function of the main effectors of cell cycle regulation (retinoblastoma protein–RB, E2Fs, c-Myc), as reviewed below.

In the mammalian cell cycle, normal cells exert a tight regulation of the G1-to-S phase transition, whereas in cancer cells, this transition is a main objective for dysregulation. RB is one of the earlier identified tumor suppressors [146]. Hence, RB activity is deregulated in a broad spectrum of tumors [147]. RB has abundant binding partners [148], the most important of which is the transcriptional factor E2F, which controls a range of genes important for entry into the S phase of the cell cycle. Hypophosphorylated RB binds to E2F complexes and represses the expression of S-phase genes, retaining cells in G1. CDK-dependent phosphorylation promotes the release of RB from E2F and cell cycle progression [149].

In mammals, lamin A regulates G1-to-S phase transition by affecting the RB pathway [150–154], since A-type lamins are required for proper RB function. In detail, A-type lamins promote RB-dependent transcriptional repression of E2F target genes. Furthermore, A-type lamins influence three other machineries regulating RB function: RB phosphorylation, RB localization, and RB protein stability [155,156]. The effect of A-type lamins in RB protein stability, together with the altered activity of ubiquitin ligase components detected in cells expressing mutant forms of lamin A, raise the possibility that A-type lamins work as coordinators of nuclear proteasome function [157].
The RB pathway is further implicated in telomere regulation and cell senescence and cell differentiation in multiple lineage, DNA replication, and DNA-damage-activated checkpoint pathways (among others) [147], further linking A-type lamins to all of these processes. Supporting the implication of lamins in the regulation of DNA replication, intranuclear A-type lamins have been shown to associate with initial sites of DNA synthesis upon S-phase entry [158]. In immortalized cells, lamin B was localized to intranuclear sites of late S-phase replication [159], and disruption of the lamin structure impairs initiation of DNA synthesis [160–162].

More than A-type lamins, nuclear γ-tubulin also regulate the transcriptional activity of E2F [163]. Nuclear γ-tubulin and E2F concur in a DNA-binding complex isolated from E2F-regulated promoters [163]. In addition, RB1 and γ-tubulin proteins mutually control their expression, and, in several tumors, an inverse correlation in their expression levels was reported for γ-tubulin and RB1 [164]. Interestingly, γ-tubulin also interacts with lamin B recruitment at post-mitotic NE reassembly, as previously mentioned [123].

Other A-type lamin functions may promote G1 maintenance, since RB–lamin A/C and extracellular signal-regulated kinase (ERK)1/2–lamin A/C complexes are mutually exclusive. When G1 arrested cells are stimulated with serum, c-Fos protein is phosphorylated by mitogen activated protein kinase (MAPK) ERK1/2. Phosphorylated c-Fos associates with c-Jun to form a dimeric Activating Protein 1 (AP-1) transcription activator complex that mediates cell cycle progression [165]. ERK1/2-dependent lamin A/C binding upon serum stimulation releases RB from the RB–lamin A/C complex, thereby promoting cell cycle progression.

The NPC-associated sentrin-specific protease 1 (SENP1) is also reported to influence cell cycle progression by regulating the expression of CDK inhibitors [166,167].

Regarding c-Myc-encoded proteins, their association with the nuclear matrix was first described in avian nuclei [168], and more recently, it was shown that the stabilized and active form of the MYC protein (pS62MYC) is enriched at the nuclear periphery of mammalian cell lines in proximity with lamin A/C [169], and precisely localizes to the nuclear pore basket [170]. However, how this regulates transcription and cellular functions remains to be elucidated.

Concerning cell senescence, the NE and the RB pathway have been implicated in an oncogenic signaling that triggers a cell cycle arrest program, i.e., oncogene-induced senescence (OIS). A dramatic reorganization of heterochromatin occurs in OIS. OIS cells lose heterochromatin interactions with lamin B1 through lamina-associated domains (LADs) [171,172], therefore, heterochromatin leaves the nuclear periphery and appears as internal senescence-associated heterochromatin foci (SAHFs) [173]. The activation of the pRB pathway is implicated in the appearance of SAHFs [173], while the NE is also implicated via laminB1 and LBR [174,175] and nuclear pore density [176]. In addition, the composition and density of the NPC changes during differentiation and tumorigenesis [19,46,176–178].

With respect to the maintenance of telomere metabolism [179] and DNA damage, in human cells, mutant LMNA has been connected to p53 engagement due to enhanced DNA damage (reviewed in [180]). Indeed, retinoblastoma independent regulation of cell proliferation and senescence by the p53-p21 axis was reported in lamin A/C-depleted cells [181].

In apoptosis, both via the intrinsic and extrinsic pathways, lamins have been described as cleaved by caspases 3 and 6. Indeed, the cleavage of lamin proteins by caspases is a necessary step in apoptosis that allows for nuclear membrane degradation to proceed, followed by chromatin condensation in a murine model [182]. In human and avian cells, A-type lamins are cleaved at their conserved VEID site by caspase 6, while B-type are cleaved at their VEVD site by caspase 3 [183–185]. In contrast, an active role of lamins in the induction, but also the prevention of apoptosis is beginning to emerge (reviewed in [186]). In cancer, apoptosis is usually reported. Strikingly, apoptosis levels are increased in the most highly proliferative tumors compared to lowly proliferative tumors. The role of lamins, if any, behind these altered levels is still unclear. One possibility would be that the amount of lamins present and the accessibility of lamins for caspases could delay the onset of apoptosis in certain tumors [187].
In metazoan, an estimated 10% of total A-type lamins localize throughout the nucleoplasm in a mobile and dynamic pool, most likely in association with LAP2α [98,162,188]. Studies on the role of A-type lamins and the RB pathway do not discriminate between these two lamin pools. However, the LAP2α promoter was reported to bind E2F1 and c-Myc [65], E2F1 and E2F4 [66], E2F3b [67], and E2F7 [68], as assessed by chromatin immunoprecipitation and microarray techniques. Indeed, LAP2α expression aligns with the phase of the cell cycle, and its overexpression has been described in various human tumor samples and cancer-derived cell lines (reviewed in [189]).

A last example is the INM protein emerin, which has been linked to cell cycle misregulation in microarray studies in X-linked EDMD patient samples where the lack of emerin disrupts the RB pathway [190].

In summary, several elements of the NE interact with the regulators of cell cycle progression, cell senescence, telomer metabolism and apoptosis. Therefore, perturbations in NE elements affecting the strict control of these interactions can lead to the development of cancer.

3.2. Nuclear Envelope in Cell Signaling

Extracellular or cytoplasmic stimuli reach the nuclear interior through signal transduction with the aim of inducing a cellular response, resolved mainly through variations in gene expression. The following signaling cascades from the plasma membrane count with an additional layer of regulation at the NE: MAPK signaling, AKT-Mammalian Target of Rapamycin signaling, Notch signaling, Wnt signaling, NF-κB signaling, and transforming growth factor-β (TGFβ) signaling. This control comes from the fact that signaling cascades need to get into the nucleus through the NPCs and that several effectors (β-catenin and smads) are sequestered at the NE by multiple NETs, as described below.

3.2.1. Lamins in Cell Signaling

The MAPK pathway dysregulation has been shown to be a driving factor in oncogenesis [191–193]. This pathway involves three main arms: ERK1/2, c-Jun NH2-terminal kinase (JNK), and p38 [194,195]. Phosphorylated MAPKs transit to specific subcellular compartments, such as the nucleus, to elicit their function. The localization of phosphorylated MAPKs to the nucleus is predominantly mediated by binding interactions with sequestering anchors and components of the nuclear transport machinery. In the nucleus, phosphorylated MAPKs regulate various cellular processes from growth to apoptosis, passing through differentiation, inflammation, metabolism, stress response, and autophagy [194–196]. An ERK1/2-activated transcription factor promoting cell cycle progression is, as previously introduced, c-Fos. c-Fos activity is suppressed by a sequestering interaction with lamin A that localizes this transcription factor to the NE [197]. Furthermore, ERK1/2 colocalizes with c-Fos at the NE by means of binding lamin A and this leads to the phosphorylation and release of c-Fos from the NE in mammalian models [198]. In addition, enhanced nuclear accumulation of ERK1/2 and JNK was reported in mice carrying a missense mutation that causes autosomal dominant EDMD and in mice expressing a truncated form of lamin A (lamin AΔ8-11). In mammals, lamin A itself can be phosphorylated by AKT, by which its expression can be regulated [202,203].

The AKT-mammalian target of rapamycin (mTOR) signaling pathway is frequently co-activated along with ERK1/2 in response to growth factor signaling and in various forms of cancer [200,201]. Alterations in A-type lamins have been shown to trigger AKT-mTOR signaling in the above-mentioned mouse model of autosomal dominant EDMD and in mice expressing a truncated form of lamin A (lamin AΔ8-11). In mammals, lamin A itself can be phosphorylated by AKT, by which its expression can be regulated [202,203].

Hutchinson–Gilford progeria syndrome (HGPS) is mainly linked to a silent mutation LMNA. This G608G mutation in LMNA triggers a cryptic splice site and as a result, the progerin protein is produced. Progerin is a truncated form of prelamin A where the last C-terminal 50 amino acids are missing [204,205]. Several signaling pathways are imbalanced in HGPS due to the presence of progerin:

- One of them is Notch signaling, which is altered in many cancers and is thought to maintain cancer stem cells [206]. This highly conserved juxtacrine signaling is involved in regulating cell fate specification and it is altered in the mesenchymal stem cell lineage in HGPS.
• Additionally, the deposition of extracellular matrix (ECM) is altered in children with HGPS, mainly due to the reduced activity of the TCF4/LEF1 complex, a key downstream effector of the Wnt signaling pathway. Progerin expression decreases the expression and nuclear accumulation of LEF1 [207].

• NF-κB signaling functions as a sensor for genotoxic stress [208] and LmnaG609G/G609G mice (murine equivalent of LMNA G608G/G608G mutation) exhibit activated NF-κB signaling through ATM-NEMO-mediated mechanisms [209].

3.2.2. LEM Proteins in Cell Signaling

Several LEM proteins have been shown to recruit and regulate the transcriptional co-activators of the Wnt and the TGFβ signaling pathways: β-catenin and Smads, respectively:

• Emerin is a binding partner of β-catenin. Upon activation of Wnt signaling, β-catenin escapes proteasomal degradation and accumulates in the nucleus. Emerin binding to β-catenin inhibits its activity by facilitating nuclear export, thereby preventing accumulation in the nucleus in human fibroblasts [210].

• MAN1 binds to receptor-mediated Smads (rSmads), intracellular mediators of the TGF-β, and bone morphogenic protein (BMP) signaling. rSmads play an intimate role in cancer metastasis [211]. The C-terminus of MAN1 sequesters rSmads at the inner nuclear membrane, thereby preventing their ability to migrate to gene enhancer regions and activate transcription [212–214].

In brief, several elements of the NE provide an additional stage of regulation of signaling pathways that control proliferation and, in turn, potential points whose dysregulation may generate the unrestrained proliferation typical of tumor transformation.

4. Nuclear Envelope Regulation of the Genome

Tumor cells are characterized by massive changes in both the pattern of gene expression and in genome organization, the most critical of these being chromosome translocations and DNA damage/breaks. Since the link between chromosome translocations and tumorigenesis has been established in humans [215], checking karyotypes for translocations has become a standard diagnostic tool for many cancer types. Physically, chromosome translocations need DNA damage and repair systems to occur, but the course of chromosome translocations varies upon aspects of higher order chromosome structure in the nucleus. Particularly, this refers to chromosome positioning patterns. These patterns are preserved in a tissue-specific manner and might explain the preference for certain chromosomal translocations in certain tumor types. Indeed, in a particular tissue where the tumor arises, chromosomes adjacent one to another in the interphase nucleus will be involved in the chromosomal translocations distinctive of this tumor type [216].

4.1. Spatial Genome Organization Directed from the Nuclear Periphery

A direct physical contact between the NE and the chromatin was first suggested by microscopy observations [217,218]. Later biochemical experiments further supported that contact. In detail, chromatin components were retained and detected when extracting and purifying the NE using high ionic strength buffers [219].

More recently, new evidence in support of this view has come from specific chromatin epigenetic modifications. Heterochromatin is modified with histone H3 lysine 9 dimethylation and trimethylation (H3K9me2 and H3K9me3). In higher eukaryotes, antibodies against H3K9me2 reveal the distribution of heterochromatin close to the NE. Antibodies against H3K9me3, in contrast, stain internal heterochromatic domains in accordance with the presence of H3K9me3 in telomeres and centromeres [220]. These data agree with earlier biochemical and microscopic observations describing distinct subpopulations of HP1α at the NE in both mouse and human cells [221].
In addition, several chromatin-binding partners of NETs precisely colocalize with transcriptionally silenced chromatin \[90,222,223\]. Indeed, these partners are indispensable for heterochromatin distribution at the nuclear periphery in a specific pattern \[50,224\]. Mostly, the NET SUN proteins have been reported to mediate tethering to the NE of telomere and centromere in several systems \[225–229\].

4.2. Tethering of Chromosomes and Loci to the NE

NETs tissue-specific expression was previously described above. The specific collection of NETs in a cell type seems to be crucial in determining the position of chromosomes to the NE. Hence, when NETs preferentially expressed in muscle cells, fat, or liver are exogenously expressed in fibroblasts, chromosomes reposition to the NE. In liver cells, knock-down of liver-specific NETs 45 and 47 triggered the release of several chromosomes from the NE \[230\]. Strikingly, different NETs might affect the location of different subsets of chromosomes, raising the tempting possibility that NETs are the actual endogenous players behind a tissue-specific spatial genome organization \[230\].

4.3. Chromatin Lipid Fraction

The presence of phospholipids as a component of chromatin is well-documented and many enzymes, such as sphingomyelin-synthase (SMS) and sphingomyelinase (SMase), have been located in the INM \[231\]. Many different roles have been attributed to the intranuclear lipid fraction in relation to cell proliferation and differentiation.

Lipid microdomains, rich in Sphingomyelin (SM) and cholesterol (CHO), present in the INM are called nuclear lipid microdomains (NLMs). In the mammal liver, NLMs act as a resting place for active chromatin and transcription factors by regulating DNA \[232\] and RNA \[8,233\] synthesis.

SM is highly represented inside the nucleus and changes in its amount in different cell physiological states. These variations might reflect the nuclear presence of a SMase, which hydrolyzes SM to ceramide and phosphorylcholine (PPC), and a SMS, which synthesizes SM from ceramide and PPC derived from PC (reviewed by \[231\]). The prognostic value of SMS levels in certain types of human cancer is just beginning to be understood \[234,235\]. In the S-phase, the decondensation of chromatin is favored by a decrease of SM due to the increased activity of SMase. The decrease of SM favors the increase of the CHO free fraction. In turn, CHO enhances the activities of cyclin-dependent kinases needed for the entrance into the S-phase. In the contrast, inhibition of CHO synthesis induces cell cycle arrest in the S-phase with decreased expression of cdk2 and cdk4. At the end of the S-phase, an increase in SM is observed when SMS increases its activity whereas that of SMase decreases. Indeed, the restoration of the amount of SM marks the transition moment to the G2 phase (reviewed by \[231\]).

To recapitulate, NE actively participates in the distribution and organization of the genome within the nucleus, by means of NETs and specific membrane lipids. In the early stages of cancer, alterations in this distribution can result in chromosomal translocations and altered gene expression.

5. The Nuclear Envelope Link to Cell Migration and Metastasis and Its Use in Cancer Prognosis

The differences in cell morphology in human tumor cells were first reported in the mid-1800s \[236,237\]. Diagnostic features include differences in cell size and shape, number, and size of the nuclei, and loss of adherence to adjacent cells in biopsies \[236,238\]. In the mid-1900s, Papanicolau’s smear test was established as a routine technique for cervical cancer detection and is used today in a wide range of specimens, as outlined above \[2,3,239\]. Interestingly, in current computer-assisted diagnostic protocols, the diagnostic parameters employed are still largely morphological and nucleus centric, as they were 160 years ago. Focusing on the nucleus, the trained eye of the cytopathologist observes those features: Karyoplasmic ratio, nuclear roundness, NE smoothness, chromatin distribution, and the presence of NE invaginations and grooves (reviewed in \[240\]).
5.1. Nuclear Mechanics

Remarkably, while different cancers arise through different mechanisms and from different tissues, the above-mentioned nuclear abnormalities are mostly still common in all cancers, suggesting that nuclear structural alterations are functionally relevant in carcinogenesis. Mechanistically, the nucleoskeleton–cytoskeleton connection has profound effects on cell polarization, nuclear positioning, nuclear migration, and cell migration [241,242].

In addition to the implication of oncogenes and tumor-suppressor genes, the role of the physical constraints of tumor cells and their microenvironment has been explored within the last 15 years. Cancer cells show reduced stiffness, generate increased contractile forces, and are strongly influenced by their biomechanical environment (reviewed in [243]). Physical measurement can be used to distinguish nontumorigenic cells from cancer cells, and highly invasive from less invasive cells among those later [244].

The nucleus is both elastic and viscoelastic. Both behaviors are due to the nuclear lamina and the nuclear interior, respectively. Typically, the nucleus is ~2–10 times stiffer when compared to the surrounding cytoplasm. Hence, both the nuclear lamina and the nuclear interior govern the mechanical deformability of the nucleus. In reference to the lamins, cells modulate their levels according to the environmental constraints. Numerous studies on mice and cells grown on different supports show a prevalence of type A lamins in situations requiring stiffness, compared to a predominance of type B lamins when elasticity is required [245–248]. Moreover, lamins participate in the transmission of mechanical forces from the cytoskeleton, as they are integrated in a membrane–protein–chromatin network that allows their physical connection with Linkers of the Nucleoskeleton to the Cytoskeleton (LINC complexes) [249]. Additionally, chromatin contributes to nuclear stiffness and viscoelastic behavior (reviewed in [250]).

The structure and composition of the NE is especially relevant in cellular mechanics and function, affecting nuclear deformability and fragility and participating in mechanotransduction signaling (reviewed in [250]). Regarding the nuclear interior, it contains more than DNA and histones. The composition of this nucleoskeleton, its function, and its relevance in cancer remain a matter of debate, while a plethora of structural proteins are present on this compartment (actin, myosin, spectrin, γ-tubulin) (reviewed in [129,250]). Nucleo-cytoskeletal coupling has been reported to occur through LINC complexes, SUN domain proteins, nesprins and other KASH domain proteins, and the INM protein Samp1 [251,252]. These nucleo-cytoskeletal coupling elements are critical to ensure the force transmission between the nucleus and cytoskeleton and the modulation of the protrusions needed for cell migration (reviewed in [250]). Moreover, direct connections of the cytoskeleton with the nucleoskeleton through the NE might be an alternative means to the NPC for signal transduction between the cytoplasm and nucleus (reviewed in [240]). Using these elements, the stimulation of integrins on the surface of intact endothelial cells, for instance, results in both the reorientation of cytoskeletal filaments, the distortion of the nucleus, and the spatial redistribution of subnuclear structures [253]. In addition, changes in nuclear organization might affect gene expression of DNA stability (reviewed in [250]). Still, one open question is whether this mechanically induced change in nuclear structure and chromatin configuration can activate specifically mechanosensitive genes [254].

The relevance of nuclear mechanics in cancer comes from the fact that the nucleus is the largest and stiffest organelle of the cell, dominating the overall cellular mechanical response when cells are subjected to large deformations, for instance, when squeezing through narrow constrictions imposed by ECM fibers and other cells [241,242,255]. The irregular nuclear morphology of cancer cells often resembles that of abnormal nuclear shapes in cells with altered NE proteins, such as A- and B-type lamins and LBR (reviewed in [250]). Presumably, changes in nuclear architecture modify the rigidity of the nucleus, and this might increase nuclear deformability to benefit metastatic processes where cells need to pass through narrow interstitial spaces or small capillaries. Transient nuclear deformations, resulting in hourglass- and cigar-shape nuclei as well as nuclear protrusions have been observed during cancer cell migration in vivo [241].
5.2. Nuclear Positioning, Nuclear Envelope Rupture and Repair, and Cancer Cell Migration

Nuclear positioning in the cytoplasm is a highly regulated process that is dynamic in space and time and is required for multiple cellular and developmental processes. Extreme examples are skeletal muscle cells with a nuclei position at the periphery and epithelial tissues where nuclei are usually away from the apical membrane (reviewed in [256]). Nuclear positioning might additionally be involved in metastatic tumor cell migration, since cell polarization is required as a prior step for proper cell migration. In the course of cell polarization, in multiple migrating cell types, a centrosome and Golgi reorientation phenomenon occurs by which these organelles become positioned between the nucleus and the future leading edge. This reorientation seems to be achieved by a rearward movement of the nucleus away from the future leading edge, whereas the centrosome stays mostly static in the center of the cell [257]. Inhibition of nuclear movement impairs cell migration (reviewed in [256]).

Several molecular entities of the nucleo-cytoskeletal coupling have been found to be required for nuclear movement prior to cell migration: Nesprins, SUN, Samp1, and transmembrane actin-associated nuclear (TAN) lines, a novel NE structures involved in force transduction during nuclear movement (reviewed in [256]). The reshaping of the NE and the rearrangement of the NE-associated cytoskeleton help to prepare the cells for directional motion [258,259]. Furthermore, recent reports in mammals have connected the movement and positioning of organelles in the cytoplasm to \( \gamma \) -tubulin protein, e.g., in the positioning of Golgi apparatus and mitochondria [260,261]. In line with this, the Leu387Pro mutation in \( \gamma \) -tubulin was shown to influence nuclear positioning in yeast cells [262]. This may be attributed to the association of nuclear and cytosolic \( \gamma \) -strings with other components of the \( \gamma \) -tubulin meshwork, such as \( \gamma \) -tubules [263], which may provide a supporting scaffold dictating the positioning of the nuclear compartment.

A long list of translocations involving nucleoporins have been described in tumors (reviewed in [65,75]). Several of them alter the normal function of the NPC and contribute to pathogenicity. NUP214–ABL fusion protein needs to be targeted to the NPC for its transforming activity [264], and NUP98 fusion proteins affect nuclear export [265]. Furthermore, nucleoporins interact with important players in cell migration [143,266–271]. For example, NUP153 contributes to cell motility and migration interacting with A-type lamins and SUN1, while NUP358 interacts with kinesin 2 to locate APC to the cell cortex [267].

Concerning NE rupture and repair, in normal cells, NE breakdown and reassembly is limited to mitosis and is precisely regulated [105]. Misseggregated chromosomes during mitotic exit can recruit their own NE to form micronuclei (MN), resulting in a NE susceptible to loss of integrity [272] and might be an objective biomarker for genomic instability in solid tumors. The irreversible NE rupture of MN can cause extensive DNA damage and promote tumorigenesis. MNs contain less NPC than the nucleus, are defective in nucleocytoplasmic transport, and replicate their DNA in an ineffective and asynchronous manner to their primary nucleus [272,273]. Furthermore, in many cancer cells, transient rupture and resealing of the NE is a common event during interphase. As a result, the nucleus and cytoplasm temporarily exchange material between them, even occasionally entrapping cytoplasmic organelles inside the nucleus. NE rupture has been further linked to the appearance of micronuclei, to the mislocalization of nucleoplasmic and cytoplasmic proteins, and to the exit of chromatin portions from the nuclear interior [274].

5.3. Nuclear Envelope Invaginations and Cancer

The NE is mainly a smooth surface, but it also presents invaginations. Those invaginations can stretch deep into the nucleoplasm, eventually crossing the nucleus entirely. High-resolution microscopy observations have revealed that aberrations in nuclear shape and size used for cancer diagnosis are probably due to large-scale invaginations of the NE that are able to traverse most or even all the nucleus (reviewed in [275]). These invaginations have been named the nucleoplasmic reticulum (NR) for their morphological similarity to the ER. NR invaginations are called type I when the INM alone is involved, while NR invaginations are called type II when both the INM and ONM
invaginate into the nucleoplasm. Type II invaginations may enclose microtubules, microfilaments, and even mitochondria in their cytoplasmic core [276,277]. Interestingly, a potential implication of γ-tubulin tubules in nuclear invagination may be further investigated, since a recent report showed that γ-tubules could also pass through the center of the nucleus [261]. The NR is observed in nuclei from various normal and abnormal tissues [278], as well as in cells grown in 2D and 3D cultures, including many tumor cell types, such as brain, breast, kidney, bladder, prostate, and ovary [279,280]. Appearance of the NR may occur both after mitosis, during NE reassembly, and without mitosis, i.e., de novo in interphase cell nuclei. Then, NR is commonly maintained throughout interphase and, in specific cell types, it can show heritable patterns [281–283]. The actual mechanisms by which this new nuclear structural component, the NR, affects cell function in normal and cancer cells are still under investigation. However, the diagnostic and prognostic significance of irregularities and invaginations of the NE in cancer cells are indisputable.

6. Conclusions

The specific traits of nuclear cell morphology in tumor cells have been used in the last 150 years to evaluate the diagnosis and prognosis of human cancer. Although the NM, attached NETs, and other proteins have been found to be implicated in this morphology (e.g., type A/C and type B lamins, nucleoporins, γ-tubulin), further research is needed to precisely define the molecular entities behind the alterations in the number, size, and shape of nuclei in tumor cells.

Author Contributions: M.A.-K. wrote and revised the paper, provided guidance and funding; C.A.R. conceived and designed the manuscript, collected the relevant references, wrote and revised the paper.

Funding: This research was funded by the Swedish Cancer Society (grant number CAN2016/369), Skane University Hospital in Malmö Cancer Research Fund (grant number 20151209), the Swedish Childhood Cancer Foundation (grant number PR2016-0084), the Crafoordska Foundation (grant number 20180670), the European Commission Seventh Framework Programme (agreement number PIEF-GA-2013-627441) and the Balearic Island Government and European Social Fund (grant number PD/036/2016).

Acknowledgments: We apologize to all authors whose work could not be cited due to space constraints. The authors thank C. Hoffmann for editorial assistance.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| APC          | Adenomatous polyposis coli (APC) |
| BAF          | Barrier-to- autointegration-factor |
| BMP          | Bone morphogenic protein |
| CCT          | Chaperonin containing TCP-1 |
| CDK          | Cyclin-dependent kinase |
| CHO          | Cholesterol |
| ECM          | Extracellular matrix |
| EDMD         | Emery-Dreifuss muscular dystrophy |
| ER           | Endoplasmic reticulum |
| ERK1/2       | Extracellular signal-regulated kinase 1/2 |
| ESCRT        | Endosomal sorting complexes required for transport |
| FG           | Phenylalanine and glycine |
| HGPS         | Hutchinson-Gilford progeria syndrome |
| HP1          | Heterochromatin protein 1 |
| INM          | Inner nuclear membrane |
| JNK          | c-Jun NH2-terminal kinase |
| LADs         | Lamina-associated domains |
| LBR          | Lamin B receptor |
| MAPK         | Mitogen Activated Protein Kinase |
MN Micronuclei
NE Nuclear envelope
NETs Nuclear envelope transmembrane proteins
NLMs Nuclear lipid microdomains
NPCs Nuclear pore complexes
NR Nucleoplasmic reticulum
OIS Oncogene-induced senescence
ONM Outer nuclear membrane
PPC Phosphorylcholine
RB Retinoblastoma
SAHFs Senescence-associated heterochromatin foci
SENP1 Sentrin-specific protease 1
SM Sphingomyelin
SMS Sphingomyelin-synthase
TAN lines Transmembrane actin-associated nuclear lines
TGFβ Transforming growth factor-β

References
1. Papanicolaou, G.N. A new procedure for staining vaginal smears. *Science* **1942**, *95*, 438–439. [CrossRef] [PubMed]
2. Morrison, L.F.; Hopp, E.S.; Wu, R. II Diagnosis of Malignancy of the Nasopharynx. Cytological Studies by the Smear Technic. *Ann. Otol. Rhinol. Laryngol.* **1949**, *58*, 18–32. [CrossRef]
3. Montgomery, P.W.; Von Haam, E. A Study of the Exfoliative Cytology in Patients with Carcinoma of the Oral Mucosa. *J. Dent. Res.* **1951**, *30*, 308–313. [CrossRef] [PubMed]
4. Callan, H.G.; Tomlin, S.G. Experimental studies on amphibian oocyte nuclei I. Investigation of the structure of the nuclear membrane by means of the electron microscope. *Proc. R. Soc. Lond. Ser. B Biol. Sci.* **1950**, *137*, 367–378.
5. Tapley, E.C.; Starr, D.A. Connecting the nucleus to the cytoskeleton by SUN–KASH bridges across the nuclear envelope. *Curr. Opin. Cell Biol.* **2013**, *25*, 57–62. [CrossRef]
6. Suntharalingam, M.; Wente, S.R. Peering through the Pore: Nuclear Pore Complex Structure, Assembly, and Function. *Dev. Cell* **2003**, *4*, 775–789. [CrossRef]
7. Schirmer, E.C.; Gerace, L. The nuclear membrane proteome: extending the envelope. *Trends Biochem. Sci.* **2005**, *30*, 551–558. [CrossRef]
8. Ciascianelli, G.; Villani, M.; Tosti, M.; Marini, F.; Bartoccini, E.; Viola Magni, M.; Albi, E. Lipid Microdomains in Cell Nucleus. *Mol. Biol. Cell* **2008**, *19*, 5289–5295. [CrossRef]
9. Ledeen, R.W.; Wu, G. Nuclear lipids: key signaling effectors in the nervous system and other tissues. *J. Lipid Res.* **2004**, *45*, 1–8. [CrossRef]
10. Choi, J.C.; Worman, H.J. Nuclear Envelope Regulation of Signaling Cascades. *Adv. Exp. Med. Biol.* **2014**, *773*, 187–206.
11. Aaronson, R.P.; Blobel, G. Isolation of nuclear pore complexes in association with a lamina. *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 1007–1011. [CrossRef] [PubMed]
12. Maeno, H.; Sugimoto, K.; Nakajima, N. Genomic Structure of the Mouse Gene (Lmnb1) Encoding Nuclear Lamin B1. *Genomics* **1995**, *30*, 342–346. [CrossRef]
13. Gerace, L.; Burke, B. Functional Organization of the Nuclear Envelope. *Annu. Rev. Cell Biol.* **1988**, *4*, 335–374. [CrossRef] [PubMed]
14. Robson, M.I.; Le Thanh, P.; Schirmer, E.C. NETs and cell cycle regulation. *Adv. Exp. Med. Biol.* **2014**, *773*, 165–185.
15. Ellenberg, J.; Lippincott-Schwartz, J. Dynamics and Mobility of Nuclear Envelope Proteins in Interphase and Mitotic Cells Revealed by Green Fluorescent Protein Chimeras. *Methods* **1999**, *19*, 362–372. [CrossRef]
16. Haraguchi, T.; Koujin, T.; Hayakawa, T.; Kaneda, T.; Tsutsumi, C.; Imamoto, N.; Akazawa, C.; Sukegawa, J.; Yoneda, Y.; Hiraoka, Y. Live fluorescence imaging reveals early recruitment of emerin, LBR, RanBP2, and Nup153 to reforming functional nuclear envelopes. *J. Cell Sci.* **2000**, *113*, 779–794.
17. Cronshaw, J.M.; Krutchinsky, A.N.; Zhang, W.; Chait, B.T.; Matunis, M.J. Proteomic analysis of the mammalian nuclear pore complex. *J. Cell Biol.** 2002, 158, 915–927. [CrossRef] [PubMed]

18. Strambio-De-Castilla, C.; Niepel, M.; Rout, M.P. The nuclear pore complex: bridging nuclear transport and gene regulation. *Nat. Rev. Mol. Cell Biol.** 2010, 11, 490–501. [CrossRef]

19. Raices, M.; D’Angelo, M.A. Nuclear pore complex composition: a new regulator of tissue-specific and developmental functions. *Nat. Rev. Mol. Cell Biol.** 2012, 13, 687–699. [CrossRef]

20. Terry, L.J.; Wente, S.R. Flexible Gates: Dynamic Topologies and Functions for FG Nucleoporins in Nucleocytoplasmic Transport. *Eukaryot. Cell** 2009, 8, 1814–1827. [CrossRef]

21. Ungricht, R.; Kutay, U. Mechanisms and functions of nuclear envelope remodelling. *Nat. Rev. Mol. Cell Biol.** 2017, 18, 229–245. [CrossRef]

22. D’Angelo, M.A.; Anderson, D.J.; Richard, E.; Hetzer, M.W. Nuclear pores form de novo from both sides of the nuclear envelope. *Science** 2006, 312, 440–443. [CrossRef]

23. Newport, J.W.; Wilson, K.L.; Dunphy, W.G. A lamin-independent pathway for nuclear envelope assembly. *J. Cell Biol.** 1990, 111, 2247–2259. [CrossRef]

24. Webster, M.; Witkin, K.L.; Cohen-Fix, O. Sizing up the nucleus: nuclear shape, size and nuclear-envelope assembly. *J. Cell Sci.** 2009, 122, 1477–1486. [CrossRef]

25. Brandt, A.; Papagiannouli, F.; Wagner, N.; Wilsch-Bräuninger, M.; Braun, M.; Furlong, E.E.; Loserth, S.; Wenzl, C.; Pilot, F.; Vogt, N.; et al. Developmental control of nuclear size and shape by Kugelkern and Kurzkern. *Curr. Biol.** 2006, 16, 543–552. [CrossRef]

26. Dittmer, T.A.; Stacey, N.J.; Sugimoto-Shirasu, K.; Richards, E.J. LITTLE NUCLEI genes affecting nuclear pore morphology in Arabidopsis thaliana. *Plant Cell** 2007, 19, 2793–2803. [CrossRef]

27. Doucet, C.M.; Hetzer, M.W. Nuclear pore biogenesis into an intact nuclear envelope. *Chromosoma** 2010, 119, 469–477. [CrossRef]

28. Toyama, B.H.; Savas, J.N.; Park, S.K.; Harris, M.S.; Ingolia, N.T.; Yates, J.R.; Hetzer, M.W. Identification of long-lived proteins reveals exceptional stability of essential cellular structures. *Hum. Pathol.** 2002, 33, 536–544. [CrossRef]

29. Schneider, J.; Moragues, D.; Martínez, N.; Romero, H.; Jiménez, E.; Pontón, J. Cross-reactivity between Candida albicans and human ovarian carcinoma as revealed by monoclonal antibodies PA10F and C6. *Br. J. Cancer** 1998, 77, 1015–1020. [CrossRef] [PubMed]

30. Martínez, N.; Alonso, A.; Moragues, M.D.; Pontón, J.; Schneider, J. The nuclear pore complex protein Nup88 is overexpressed in tumor cells. *Cancer Res.** 1999, 59, 5408–5411.

31. Gould, V.E.; Orucevic, A.; Zentgraf, H.; Gattuso, P.; Martínez, N.; Alonso, A. Nup88 (karyoporin) in human malignant neoplasms and dysplasias: correlations of immunostaining of tissue sections, cytologic smears, and immunoblot analysis. *Hum. Pathol.** 2002, 33, 536–544. [CrossRef] [PubMed]

32. Agudo, D.; Gómez-Esquer, F.; Martínez-Arribas, F.; Núñez-Villar, M.J.; Pollán, M.; Schneider, J. Nup88 mRNA overexpression is associated with high aggressiveness of breast cancer. *Int. J. Cancer** 2004, 108, 717–720. [CrossRef] [PubMed]

33. Knoess, M.; Kurz, A.K.; Goreva, O.; Bektas, N.; Breuhahn, K.; Odenthal, M.; Schirmacher, P.; Dienes, H.P.; Bock, C.T.; Zentgraf, H.; et al. Nucleoporin 88 expression in hepatitis B and C virus-related liver diseases. *World J. Gastroenterol.** 2006, 12, 5870–5874. [CrossRef] [PubMed]

34. Zhang, Z.-Y.; Zhao, Z.-R.; Jiang, L.; Li, J.-C.; Gao, Y.-M.; Cui, D.-S.; Wang, C.-J.; Schneider, J.; Wang, M.-W.; Sun, X.-F. Nup88 expression in normal mucosa, adenoma, primary adenocarcinoma and lymph node metastasis in the colorectum. *Tumour Biol. J. Int. Soc. Oncodev. Biol. Med.** 2007, 28, 93–99. [CrossRef] [PubMed]

35. Brustmann, H.; Hager, M. Nucleoporin 88 expression in normal and neoplastic squamous epithelia of the uterine cervix. *Ann. Diagn. Pathol.** 2009, 13, 303–307. [CrossRef] [PubMed]

36. Schneider, J.; Martínez-Arribas, F.; Torrejón, R. Nup88 expression is associated with myometrial invasion in endometrial carcinoma. *Int. J. Gynecol. Cancer Off. J. Int. J. Gynecol. Cancer Soc.** 2010, 20, 804–808. [CrossRef]

37. Simon, D.N.; Rout, M.P. Cancer and the Nuclear Pore Complex. *Adv. Exp. Med. Biol.** 2014, 773, 285–307.

38. Johannessen, J.V.; Sobrinho-Simões, M.; Finseth, I.; Pilström, L. Papillary carcinomas of the thyroid have pore-deficient nuclei. *Int. J. Cancer** 1982, 30, 409–411. [CrossRef]

39. Czerniak, B.; Koss, L.G.; Sherman, A. Nuclear pores and DNA ploidy in human bladder carcinomas. *Cancer Res.** 1984, 44, 3752–3756.
40. Sugie, S.; Yoshimi, N.; Tanaka, T.; Mori, H.; Williams, G.M. Alterations of nuclear pores in preneoplastic and neoplastic rat liver lesions induced by 2-acetylaminofluorene. Carcinogenesis 1994, 15, 95–98. [CrossRef]
41. Lewin, J.M.; Lwaleed, B.A.; Cooper, A.J.; Birch, B.R. The direct effect of nuclear pores on nuclear chemotherapeutic concentration in multidrug resistant bladder cancer: the nuclear sparing phenomenon. J. Urol. 2007, 177, 1526–1530. [CrossRef]
42. Korfali, N.; Wilkie, G.S.; Swanson, S.K.; Srseen, V.; de las Heras, J.; Batrakou, D.G.; Malik, P.; Zuleger, N.; Kerr, A.R.W.; Florens, L.; et al. The nuclear envelope proteome differs notably between tissues. Nucleus 2012, 3, 552–564. [CrossRef]
43. Mattout-Drubezki, A.; Gruenbaum, Y. Dynamic interactions of nuclear lamina proteins with chromatin and transcriptional machinery. Cell. Mol. Life Sci. 2003, 60, 2053–2063. [CrossRef] [PubMed]
44. Barton, L.J.; Soshnev, A.A.; Geyer, P.K. Networking in the nucleus: a spotlight on LEM-domain proteins.
45. Mattout, A.; Pike, B.L.; Towbin, B.D.; Bank, E.M.; Gonzalez-Sandoval, A.; Stadler, M.B.; Meister, P.; Gasser, S.M. An EMDM mutation in C. elegans lamin blocks muscle-specific gene relocation and compromises muscle integrity. Curr. Biol. 2011, 21, 1603–1614. [CrossRef]
46. Rodriguez-Bravo, V.; Pippa, R.; Song, W.-M.; Carceles-Cordon, M.; Dominguez-Andres, A.; Fujimura, N.; Woo, J.; Koh, A.P.; Ertel, A.; Lokareddy, R.K.; et al. Nuclear Pores Promote Lethal Prostate Cancer by Increasing POM121-Driven E2F1, MYC, and AR Nuclear Import. Cell 2018, 174, 1200–1215. [CrossRef]
47. Dauer, W.T.; Worman, H.J. The nuclear envelope as a signaling node in development and disease. Dev. Cell 2009, 17, 626–638. [CrossRef]
48. Kind, J.; van Steensel, B. Genome–nuclear lamina interactions and gene regulation. Curr. Opin. Cell Biol. 2010, 22, 320–325. [CrossRef] [PubMed]
49. Heald, R.; McKeon, F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. Cell 1990, 61, 579–589. [CrossRef]
50. Peter, M.; Nakagawa, J.; Dorée, M.; Labbé, J.C.; Nigg, E.A. In vitro disassembly of the nuclear lamina and M phase-specific phosphorylation of lamins by cdc2 kinase. Cell 1990, 61, 591–602. [CrossRef]
51. Burke, B.; Stewart, C.L. The nuclear lamins: flexibility in function. Nat. Rev. Mol. Cell Biol. 2013, 14, 13–24. [CrossRef]
52. Gerace, L.; Blobel, G. The Nuclear Envelope Lamina is Reversibly Depolymerized during Mitosis: Cell. Available online: https://www.cell.com/cell/pdf/0092-8674(80)90409-2.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2F009286740904092%3Fshowall%3Dtrue (accessed on 10 March 2019).
53. Heald, R.; McKeon, F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. Cell 1990, 61, 579–589. [CrossRef]
54. Heald, R.; McKeon, F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. Cell 1990, 61, 579–589. [CrossRef]
55. Ward, G.E.; Kirschner, M.W. Identification of cell cycle-regulated phosphorylation sites on nuclear lamin C. J. Biol. Chem. 2007, 282, 18268–18276. [CrossRef] [PubMed]
56. Pyrpasopoulou, A.; Meier, J.; Maisen, C.; Simos, G.; Georgatos, S.D. The lamin B receptor (LBR) provides essential chromatin docking sites at the nuclear envelope. Embo J. 1996, 15, 7108–7119. [CrossRef]
57. Heald, R.; McKeon, F. Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. Cell 1990, 61, 579–589. [CrossRef]
58. Peter, M.; Nakagawa, J.; Dorée, M.; Labbé, J.C.; Nigg, E.A. In vitro disassembly of the nuclear lamina and M phase-specific phosphorylation of lamins by cdc2 kinase. Cell 1990, 61, 591–602. [CrossRef]
59. Ward, G.E.; Kirschner, M.W. Identification of cell cycle-regulated phosphorylation sites on nuclear lamin C. J. Biol. Chem. 2007, 282, 18268–18276. [CrossRef] [PubMed]
60. Pyrpasopoulou, A.; Meier, J.; Maisen, C.; Simos, G.; Georgatos, S.D. The lamin B receptor (LBR) provides essential chromatin docking sites at the nuclear envelope. Embo J. 1996, 15, 7108–7119. [CrossRef]
61. Gorjánácz, M.; Klerkx, E.P.F.; Galy, V.; Santarella, R.; López-Iglesias, C.; Askjaer, P.; Mattaj, I.W. Caenorhabditis elegans BAF-1 and its kinase VRK-1 participate directly in post-mitotic nuclear envelope assembly. *Embo J.* 2007, 26, 132–143. [CrossRef] [PubMed]

62. LaJoie, D.; Ullman, K.S. Coordinated events of nuclear assembly. *Curr. Opin. Cell Biol.* 2017, 46, 39–45. [CrossRef] [PubMed]

63. Jeganathan, K.B.; Malureanu, L.; van Deursen, J.M. The Rae1-Nup98 complex prevents aneuploidy by inhibiting securin degradation. *Nature* 2008, 453, 1036–1039. [CrossRef] [PubMed]

64. Jeganathan, K.B.; Baker, D.J.; van Deursen, J.M. Security of the mitotic spindle checkpoint. *Nat. Rev. Mol. Cell Biol.* 2010, 11, 366–370. [CrossRef] [PubMed]

65. Schellhaus, A.K.; De Magistris, P.; Antonin, W. Nuclear Reformation at the End of Mitosis. *J. Mol. Biol.* 2016, 428, 1962–1985. [CrossRef]

66. Wilkie, G.S.; Korfali, N.; Swanson, S.K.; Malik, P.; Srsen, V.; Batrakou, D.G.; de las Heras, J.; Zuleger, N.; Kerr, A.R.W.; Florens, L.; et al. Several Novel Nuclear Envelope Transmembrane Proteins Identified in Skeletal Muscle Have Cytoskeletal Associations. *Mol. Cell. Proteom.* 2011, 10, M110.003129. [CrossRef]

67. Audhya, A.; Desai, A.; Oegea, K. A role for Rab5 in structuring the endoplasmic reticulum. *J. Cell Biol.* 2007, 178, 43–56. [CrossRef]

68. Buch, C.; Lindberg, R.; Figueroa, R.; Gudise, S.; Onischenko, E.; Hallberg, E. An integral protein of the inner nuclear membrane localizes to the mitotic spindle in mammalian cells. *J. Cell Sci.* 2009, 122, 2100–2107. [CrossRef]

69. Drummond, S.; Ferrigno, P.; Lyon, C.; Murphy, J.; Goldberg, M.; Allen, T.; Smythe, C.; Hutchison, C.J. Temporal differences in the appearance of NEP-B78 and an LBR-like protein during Xenopus nuclear envelope reassembly reflect the ordered recruitment of functionally discrete vesicle types. *J. Cell Biol.* 1999, 144, 225–240. [CrossRef]
83. Hetzer, M.; Meyer, H.H.; Walther, T.C.; Bilbao-Cortes, D.; Warren, G.; Mattaj, I.W. Distinct AAA-ATPase p97 complexes function in discrete steps of nuclear assembly. *Nat. Cell Biol.* 2001, 3, 1086–1091. [CrossRef]

84. Salpingidou, G.; Reeveck, R.; Kiseleva, E.; Lyon, C.; Lane, B.; Fusie, K.; Golebiewska, A.; Drummond, S.; Allen, T.D.; Ellis, J.A.; et al. NEP-A and NEP-B both contribute to nuclear pore formation in Xenopus eggs and oocytes. *J. Cell Sci.* 2008, 121, 706–716. [CrossRef]

85. Vigers, G.P.A.; Lohka, M.J. A distinct vesicle population targets membranes and pore complexes to the nuclear envelope in Xenopus eggs. *J. Cell Biol.* 1991, 112, 545–556. [CrossRef]

86. Vigers, G.P.; Lohka, M.J. Regulation of nuclear envelope precursor functions during cell division. *J Cell Sci* 1992, 102, 273–284.

87. Vagnarelli, P.; Earnshaw, W.C. Repo-Man-PP1: A link between chromatin remodelling and nuclear envelope reassembly. *Nucleus* 2012, 3, 138–142. [CrossRef]

88. Ohba, T.; Nakamura, M.; Nishitani, H.; Nishimoto, T. Self-organization of microtubule asters induced in Xenopus egg extracts by GTP-bound ran. *Science* 1999, 284, 1356–1358. [CrossRef] [PubMed]

89. Wiese, C.; Wilde, A.; Moore, M.S.; Adam, S.A.; Merdes, A.; Zheng, Y. Role of importin-β in coupling ran to downstream targets in microtubule assembly. *Science* 2001, 291, 653–656. [CrossRef] [PubMed]

90. Ye, Q.; Worman, H.J. Interaction between an integral protein of the nuclear envelope inner membrane and human chromodomain proteins homologous to Drosophila HP1. *J. Biol. Chem.* 1996, 271, 14653–14656. [CrossRef]

91. Ye, Q.; Callebaut, I.; Pezhman, A.; Courvalin, J.-C.; Worman, H.J. Domain-specific Interactions of Human HP1-type Chromodomain Proteins and Inner Nuclear Membrane Protein LBR. *J. Biol. Chem.* 1997, 272, 14983–14989. [CrossRef]

92. Polioudaki, H.; Kourmouli, N.; Drosou, V.; Bakou, A.; Theodoropoulos, P.A.; Singh, P.B.; Giannakouros, T.; Georgatos, S.D. Histones H3/H4 form a tight complex with the inner nuclear membrane protein LBR and heterochromatin protein 1. *Embo Rep.* 2001, 2, 920–925. [CrossRef]

93. Ulbert, S.; Platani, M.; Boue, S.; Mattaj, I.W. Direct membrane protein–DNA interactions required early in nuclear envelope assembly. *J. Cell Biol.* 2006, 173, 469–476. [CrossRef]

94. Anderson, D.J.; Hetzer, M.W. Nuclear envelope formation by chromatin-mediated reorganization of the endoplasmic reticulum. *Nat. Cell Biol.* 2007, 9, 1160–1166. [CrossRef] [PubMed]

95. Molitor, T.P.; Traktman, P. Depletion of the protein kinase VRK1 disrupts nuclear envelope morphology and leads to BAF retention on mitotic chromosomes. *Mol. Biol. Cell* 2014, 25, 891–903. [CrossRef] [PubMed]

96. Asencio, C.; Davidson, I.F.; Santarella-Mellwig, R.; Ly-Hartig, T.B.N.; Mall, M.; Wallenfang, M.R.; Mattaj, I.W.; Gorjánácz, M. Coordination of Kinase and Phosphatase Activities by Lem4 Enables Nuclear Envelope Reassembly during Mitosis. *Cell* 2012, 150, 122–135. [CrossRef] [PubMed]

97. Zhuang, P.-Y.; Zhang, J.-B.; Zhu, X.-D.; Zhang, W.; Wu, W.-Z.; Tan, Y.-S.; Hou, J.; Tang, Z.-Y.; Qin, L.-X.; Sun, H.-C. Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK19 expression in tumor. *Cancer* 2008, 112, 2740–2748. [CrossRef] [PubMed]

98. Dechat, T. LAP2 and BAF transiently localize to telomeres and specific regions on chromatin during nuclear assembly. *J. Cell Sci.* 2004, 117, 6117–6128. [CrossRef] [PubMed]

99. Chojnowski, A.; Ong, P.F.; Wong, E.S.M.; Lim, J.S.Y.; Matalif, R.A.; Navasankari, R.; Dutta, B.; Yang, H.; Liow, Y.Y.; Sze, S.K.; et al. Progerin reduces LAP2α-telomere association in hutchinson-gilford progeria. *eLife* 2015, 4, 1–21. [CrossRef]

100. Zierhut, C.; Jenness, C.; Kimura, H.; Funabiki, H. Nucleososomal regulation of chromatin composition and nuclear assembly revealed by histone depletion. *Nat. Struct. Mol. Biol.* 2014, 21, 617–625. [CrossRef]

101. Inoue, A.; Zhang, Y. Nucleosome assembly is required for nuclear pore complex assembly in mouse zygotes. *Nat. Struct. Mol. Biol.* 2014, 21, 609–616. [CrossRef]

102. Schaeley, A.; Moreno-Andre, D.; De Magistris, P.; Vollmer, B.; Antonin, W. The lysine demethylase LSD1 is required for nuclear envelope formation at the end of mitosis. *J. Cell Sci.* 2015, 128, 3466–3477. [CrossRef]

103. Vagnarelli, P.; Ribeiro, S.; Sennels, L.; Sanchez-Pulido, L.; de Lima Alves, F.; Verheyen, T.; Kelly, D.A.; Ponting, C.P.; Rappsilber, J.; Earnshaw, W.C. Repo-Man Coordinates Chromosomal Reorganization with Nuclear Envelope Reassembly during Mitotic Exit. *Dev. Cell* 2011, 21, 328–342. [CrossRef]

104. Worman, H.J.; Ostlund, C.; Wang, Y. Diseases of the nuclear envelope. *Cold Spring Harb. Perspect. Biol.* 2010, 2, a000706. [CrossRef]
105. Wandke, C.; Kutay, U. Enclosing Chromatin: Reassembly of the Nucleus after Open Mitosis. Cell 2013, 152, 1222–1225. [CrossRef]
106. Qi, W.; Yu, H. The Spindle Checkpoint and Chromosomal Stability. Genome Dyn. 2006, 1, 116–130.
107. Tran, E.J.; Wente, S.R. Dynamic Nuclear Pore Complexes: Life on the Edge. Cell 2006, 125, 1041–1053. [CrossRef]
108. Antonin, W.; Ellenberg, J.; Dultz, E. Nuclear pore complex assembly through the cell cycle: regulation and membrane organization. Fbs Lett. 2008, 582, 2004–2016. [CrossRef]
109. D’Angelo, M.A.; Hetzer, M.W. Structure, dynamics and function of nuclear pore complexes. Trends Cell Biol. 2008, 18, 456–466. [CrossRef]
110. Lim, K.-H.; Baines, A.T.; Fiordalisi, J.J.; Shipitsin, M.; Feig, L.A.; Cox, A.D.; Der, C.J.; Counter, C.M. Activation of RalA is critical for Ras-induced tumorigenesis of human cells. Cancer Cell 2005, 7, 533–545. [CrossRef]
111. Maeshima, K.; Iino, H.; Hihara, S.; Imamoto, N. Nuclear size, nuclear pore number and cell cycle. Mol. Cancer Ther. 2010, 5, 268–278. [CrossRef]
112. Schooley, A.; Vollmer, B.; Antonin, W. Building a nuclear envelope at the end of mitosis: coordinating membrane reorganization, nuclear pore complex assembly, and chromatin de-condensation. Chromosoma 2012, 121, 539–554. [CrossRef]
113. Weberruss, M.; Antonin, W. Perforating the nuclear boundary – how nuclear pore complexes assemble. J. Cell Sci. 2016, 129, 4439–4447. [CrossRef]
114. Mackay, D.R.; Makise, M.; Ullman, K.S. Defects in nuclear pore assembly lead to activation of an Aurora B-mediated abscission checkpoint. J. Cell Biol. 2010, 191, 923–931. [CrossRef]
115. Dar, A.A.; Goff, L.W.; Majid, S.; Berlin, J.; El-Rifai, W. Aurora kinase inhibitors—rising stars in cancer therapeutics? Mol. Cancer Ther. 2010, 9, 268–278. [CrossRef]
116. Doucet, C.M.; Talamas, J.A.; Hetzer, M.W. Cell cycle-dependent differences in nuclear pore complex assembly in metazoan. Cell 2010, 141, 1030–1041. [CrossRef]
117. Maeshima, K.; Iino, H.; Hihara, S.; Funakoshi, T.; Watanabe, A.; Nishimura, M.; Nakatomi, R.; Yahata, K.; Imamoto, F.; Hashikawa, T.; et al. Nuclear pore formation but not nuclear growth is governed by cyclin-dependent kinases (Cdks) during interphase. Nat. Struct. Mol. Biol. 2010, 17, 1065–1071. [CrossRef]
118. Haraguchi, T.; Kojidani, T.; Koujin, T.; Shimi, T.; Osakada, H.; Mori, C.; Yamamoto, A.; Hiraoka, Y. Live cell imaging and electron microscopy reveal dynamic processes of BAF-directed nuclear envelope assembly. J. Cell Sci. 2008, 121, 2540–2554. [CrossRef]
119. Kaufmann, T.; Kukolj, E.; Brachner, A.; Beltzung, E.; Bruno, M.; Kostrhon, S.; Opravil, S.; Hudecz, O.; Mechtler, K.; Warren, G.; et al. SIRT2 regulates nuclear envelope reassembly through ANKLE2 deacetylation. J Cell Sci 2016, 129, 4607–4621. [CrossRef]
120. Haraguchi, T.; Koujin, T.; Segura-Totten, M.; Lee, K.K.; Matsuoka, Y.; Yoneda, Y.; Wilson, K.L.; Hiraoka, Y. BAF is required for emerin assembly into the reforming nuclear envelope. J. Cell Sci. 2001, 114, 4575–4585. [CrossRef]
121. Margalit, A.; Segura-Totten, M.; Gruenbaum, Y.; Wilson, K.L. Barrier-to-autointegration factor is required to segregate and enclose chromosomes within the nuclear envelope and assemble the nuclear lamina. Proc. Natl. Acad. Sci. USA 2005, 102, 3290–3295. [CrossRef]
122. Samwer, M.; Schneider, M.W.G.; Hoefer, R.; Schmalhorst, P.S.; Jude, J.G.; Zuber, J.; Gerlich, D.W. DNA Cross-Bridging Shapes a Single Nucleus from a Set of Mitotic Chromosomes. Cell 2017, 170, 956–972. [CrossRef]
123. Rosselló, C.A.; Lindström, L.; Glindre, J.; Eklund, G.; Alvarado-Kristensson, M. Gamma-tubulin coordinates nuclear envelope assembly around chromatin. Heligov 2016, 2, e00166. [CrossRef]
124. Xue, J.Z.; Woo, E.M.; Postow, L.; Chait, B.T.; Funabiki, H. Chromatin-Bound Xenopus Dppa2 Shapes the Nucleus by Locally Inhibiting Microtubule Assembly. Dev. Cell 2013, 27, 47–59. [CrossRef] [PubMed]
125. Yokoyama, H.; Koch, B.; Walczak, R.; Ciray-Duygu, F.; González-Sánchez, J.C.; Devos, D.P.; Mattaj, I.W.; Gruss, O.J. The nucleoporin MEL-28 promotes RanGTP-dependent γ-tubulin recruitment and microtubule nucleation in mitotic spindle formation. Nat. Commun. 2014, 5, 3270. [CrossRef]
126. Pouchucq, L.; Lobos-Ruiz, P.; Araya, G.; Valpuesta, J.M.; Monasterio, O. The chaperonin CCT promotes the formation of fibrillar aggregates of γ-tubulin. Biochim. Biophys. Acta Proteins Proteom. 2018, 1866, 519–526. [CrossRef] [PubMed]
127. Batzenschlager, M.; Masoud, K.; Janski, N.; Houlné, G.; Herzog, E.; Evrard, J.-L.; Baumberger, N.; Erhardt, M.; Nominé, Y.; Kieffer, B.; et al. The GIP gamma-tubulin complex-associated proteins are involved in nuclear architecture in Arabidopsis thaliana. *Front. Plant Sci.* 2013, 4, 480. [CrossRef] [PubMed]

128. Chumov, J.; Kourová, H.; Trégelová, L.; Halada, P.; Binarová, P. Microtubular and Nuclear Functions of γ-Tubulin: Are They LINCol? *Cells* 2019, 8, 259. [CrossRef]

129. Dick, F.A.; Rubin, S.M. Molecular mechanisms underlying RB protein function. *Nat. Rev. Mol. Cell Biol.* 2013, 14, 297. [CrossRef]

130. Gimpel, P.; Lee, Y.L.; Sobota, R.M.; Calvi, A.; Koulourou, V.; Patel, R.; Mamchaoui, K.; Nédélec, F.; Shackleton, S.; Schmoranzer, J.; et al. Nesprin-1α-Dependent Microtubule Nucleation from the Nuclear Envelope via Akap450 Is Necessary for Nuclear Positioning in Muscle Cells. *Curr. Biol.* 2017, 27, 2999–3009. [CrossRef]

131. Larsson, V.J.; Jaé, A.; Ladinsky, M.S.; et al. LEM2 recruits CHMP7 for ESCRT-mediated nuclear envelope closure in eggs. *EMBO J.* 2019, 38, e107174. [CrossRef] [PubMed]

132. Clever, M.; Funakoshi, T.; Mimura, Y.; Takagi, M.; Imamoto, N. The nucleoporin ELYS is required for the assembly of a Nup93-containing complex. *Mol. Biol. Cell* 2011, 22, 1804–1816. [CrossRef] [PubMed]

133. Otsuka, S.; Bui, K.H.; Schorb, M.; Julius Hossain, M.; Politi, A.Z.; Koch, B.; Eltsov, M.; Beck, M.; Ellenberg, J. Mel28 regulates γ-Tubulin–γ-Tubulin Interactions as the Basis for the Formation of a Meshwork. *Int. J. Mol. Sci.* 2018, 19, 3249. [CrossRef]

134. Lu, L.; Ladinsky, M.; Shivay, A.; Vijayaraghavan, B.; Figueroa, R.A.; Hallberg, E. Mitotic spindle assembly and γ-tubulin localization depend on the integral nuclear membrane protein Samp1. *J Cell Sci* 2018, 131, jcs211664. [CrossRef]

135. Crabbe, L.; Cesare, A.J.; Kasuboski, J.M.; Fitzpatrick, J.A.J.; Karlseder, J. Human Telomeres Are Tethered to the Nuclear Lamina. *Nucleus* 2013, 4, 324–331. [CrossRef] [PubMed]

136. Liu, Q.; Pante, N.; Misteli, T.; Elsagga, M.; Crisp, M.; Hodzic, D.; Burke, B.; Roux, K.J. Functional association of Sun1 with nuclear pore complexes. *J. Biol. Chem.* 2007, 282, 785–798. [CrossRef]

137. Olmos, Y.; Perdrix-Rosell, A.; Carlton, J.G. Membrane Binding by CHMP7 Coordinates ESCRT-III-Dependent Nuclear Envelope Reformation. *Curr. Biol.* 2016, 26, 2635–2641. [CrossRef] [PubMed]

138. Olmos, Y.; Hodgson, L.; Mantell, J.; Verkade, P.; Carlton, J.G. ESCRT-III controls nuclear envelope reformation. *Nature* 2015, 522, 236–239. [CrossRef] [PubMed]

139. Gu, M.; Björkman, P.; Nikolova, L.; Chen, O.S.; Lajoie, D.; Redd, M.J.; Sundquist, W.I.; Frost, A.; von Appen, A.; Ladinsky, M.S.; et al. LEM2 recruits CHMP7 for ESCRT-mediated nuclear envelope closure in fission yeast and human cells. *Proc. Natl. Acad. Sci. USA* 2017, 114, E2166–E2175. [CrossRef]

140. Hawryluk-Gara, L.A.; Shibuya, E.K.; Wozniak, R.W. Vertebrate Nup53 interacts with the nuclear lamina and is required for the assembly of a Nup93-containing complex. *Mol. Biol. Cell* 2005, 16, 2382–2394. [CrossRef] [PubMed]

141. Lussi, Y.C.; Hügi, I.; Laurell, E.; Kutay, U.; Fahrenkrog, B. The nucleoporin Nup153 is interacting with nuclear lamin A. *Mol. Biol. Cell* 2011, 22, 1080–1090. [CrossRef]

142. Smythe, C.; Jenkins, H.E.; Hutchison, C.J. Incorporation of the nuclear pore basket protein nup153 into nuclear pore structures is dependent upon lamina assembly: evidence from cell-free extracts of Xenopus eggs. *Embo J.* 2000, 19, 3918–3931. [CrossRef]

143. Zhou, L.; Panté, N. The nucleoporin Nup153 maintains nuclear envelope architecture and is required for cell migration in tumor cells. *Febs Lett.* 2010, 584, 3013–3020. [CrossRef]

144. Mackay, D.R.; Elgort, S.W.; Ullman, K.S. The nucleoporin Nup153 has separable roles in both early mitotic progression and the resolution of mitosis. *Mol. Biol. Cell* 2009, 20, 1652–1660. [CrossRef] [PubMed]

145. Liu, Q.; Pante, N.; Misteli, T.; Elsagga, M.; Crisp, M.; Hodzic, D.; Burke, B.; Roux, K.J. Functional association of Sun1 with nuclear pore complexes. *J. Biol. Chem.* 2007, 178, 785–798. [CrossRef]

146. Friend, S.H.; Bernards, R.; Rogelj, S.; Weinberg, R.A.; Rapaport, J.M.; Albert, D.M.; Dryja, T.P. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* 1986, 323, 643–646. [CrossRef] [PubMed]

147. Dick, F.A.; Rubin, S.M. Molecular mechanisms underlying RB protein function. *Nat. Rev. Mol. Cell Biol.* 2013, 14, 297. [CrossRef]

148. Morris, E.J.; Dyson, N.J. Retinoblastoma protein partners. *Adv. Cancer Res.* 2001, 82, 1–54.
149. Hanahan, D.; Weinberg, R. The hallmarks of cancer. Cell 2000, 100, 57–70. [CrossRef]
150. Boban, M.; Braun, J.; Foisner, R. Laminas: ‘structure goes cycling’. Biochem. Soc. Trans. 2010, 38, 301–306. [CrossRef] [PubMed]
151. Mancini, M.A.; Shan, B.; Nickerson, J.A.; Penman, S.; Lee, W.H. The retinoblastoma gene product is a cell cycle-dependent, nuclear matrix-associated protein. Proc. Natl. Acad. Sci. USA 1994, 91, 418–422. [CrossRef]
152. Ozaki, T.; Saijo, M.; Murakami, K.; Enomoto, H.; Taya, Y.; Sakiyama, S. Complex formation between lamin A and the retinoblastoma gene product: identification of the domain on lamin A required for its interaction. Oncogene 1994, 9, 2649–2653.
153. Templeton, D.J.; Park, S.H.; Lanier, L.; Weinberg, R.A. Nonfunctional mutants of the retinoblastoma protein are characterized by defects in phosphorylation, viral oncoprotein association, and nuclear tethering. Proc. Natl. Acad. Sci. USA 1991, 88, 3033–3037. [CrossRef]
154. Mittnacht, S.; Weinberg, R.A. G1/S phosphorylation of the retinoblastoma protein is associated with an altered affinity for the nuclear compartment. Cell 1991, 65, 381–393. [CrossRef]
155. Johnson, B.R.; Nitta, R.T.; Frock, R.L.; Mounkes, L.; Barbie, D.A.; Stewart, C.L.; Harlow, E.; Kennedy, B.K. A-type lamins regulate retinoblastoma protein function by promoting subnuclear localization and preventing proteasomal degradation. Proc. Natl. Acad. Sci. USA 2004, 101, 9677–9682. [CrossRef]
156. Ellis, D.J.; Jenkins, H.; Whitfield, W.G.F.; Hutchison, C.J. GST-lamin fusion proteins act as dominant negative mutants with sites of DNA replication. J. Cell Biol. 1994, 125, 1201–1212. [CrossRef]
157. Kennedy, B.K.; Barbie, D.A.; Classon, M.; Dyson, N.; Harlow, E. Nuclear organization of DNA replication in Xenopus egg extract and reveal the function of the lamina in DNA replication. J Cell Sci 1997, 110, 2507–2518.
158. Spann, T.P.; Moir, R.D.; Goldman, A.E.; Stick, R.; Goldman, R.D. Disruption of nuclear lamin organization alters the distribution of replication factors and inhibits DNA synthesis. J. Cell Biol. 1997, 136, 1201–1212. [CrossRef]
159. Moir, R.D.; Spann, T.P.; Herrmann, H.; Goldman, R.D. Disruption of nuclear lamin organization blocks the elongation phase of DNA replication. J. Cell Biol. 2000, 149, 1179–1192. [CrossRef]
160. Hoog, G.; Zarrizi, R.; von Stedingk, K.; Jonsson, K.; Alvarado-Kristensson, M. Nuclear localization of γ-tubulin affects EF2 transcriptional activity and S-phase progression. Faseb J. 2011, 25, 3815–3827. [CrossRef]
161. Ehlén, A.; Rosselló, C.A.; Von Stedingk, K.; Höög, G.; Nilsson, E.; Pettersson, H.M.; Jirström, K.; Alvarado-Kristensson, M. Tumors with nonfunctional retinoblastoma protein are killed by reduced γ-tubulin levels. J. Biol. Chem. 2012, 287, 17241–17247. [CrossRef]
162. Verde, P.; Casalino, L.; Talotta, F.; Yaniv, M.; Weitzman, J.B. Deciphering AP-1 function in tumorigenesis: Fra-ternizing on target promoters. Cell Cycle 2007, 6, 2633–2639. [CrossRef]
163. Palancade, B.; Doye, V. Sumoylating and desumoylating enzymes at nuclear pores: underpinning their unexpected duties? Trends Cell Biol. 2008, 18, 174–183. [CrossRef] [PubMed]
164. Xu, Y.; Li, J.; Zuo, Y.; Deng, J.; Wang, L.-S.; Chen, G.-Q. SUMO-specific protease 1 regulates the in vitro and in vivo growth of colon cancer cells with the upregulated expression of CKD inhibitors. Cancer Lett. 2011, 309, 78–84. [CrossRef]
165. Eisenman, R.N.; Tachibana, C.Y.; Abrams, H.D.; Hann, S.R. V-myc- and c-myc-encoded proteins are associated with the nuclear matrix. Mol. Cell. Biol. 1985, 5, 114–126. [CrossRef] [PubMed]
166. Myant, K.; Qiao, X.; Halonen, T.; Come, C.; Laine, A.; Jianghorban, M.; Partanen, J.I.; Cassidy, J.; Ogg, E.L.; Cammareri, P.; et al. Serine 62-phosphorylated MYC Associates with nuclear lamins and its regulation by CIP2A is essential for regenerative proliferation. Cell Rep. 2015. [CrossRef]
170. Su, Y.; Pelz, C.; Huang, T.; Torkenczy, K.; Wang, X.; Cherry, A.; Daniel, C.J.; Liang, J.; Nan, X.; Dai, M.-S.; et al. Post-translational modification localizes MYC to the nuclear pore basket to regulate a subset of target genes involved in cellular responses to environmental signals. *Genes Dev.* 2018, 32, 1398–1419. [CrossRef]

171. Guelen, L.; Pagie, L.; Brasset, E.; Meuleman, W.; Faza, M.B.; Talhou, W.; Eussen, B.H.; de Klein, A.; Wessels, L.; de Laat, W.; et al. Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. *Nature* 2008, 453, 948–951. [CrossRef] [PubMed]

172. Lenain, C.; De Graaf, C.A.; Pagie, L.; Visser, N.L.; De Haas, M.; De Vries, S.S.; Peric-Hupkes, D.; Van Steensel, B.; Peeper, D.S. Massive reshaping of genome-nuclear lamina interactions during oncogene-induced senescence. *Genome Res.* 2017, 27, 1634–1644. [CrossRef]

173. Narita, M.; Núñez, S.; Heard, E.; Narita, M.; Lin, A.W.; Hearn, S.A.; Spector, D.L.; Hannon, G.J.; Lowe, S.W. Rb-mediated heterochromatin formation and silencing of E2F target genes during cellular senescence. *Cell* 2003, 113, 703–716. [CrossRef]

174. Sadaie, M.; Salama, R.; Carroll, T.; Tomimatsu, K.; Chandra, T.; Tomimatsu, K.; Chandra, T.; Young, A.R.J.; Narita, M.; Pérez-Mancera, P.A.; Bennett, D.C.; Chong, H.; et al. Redistribution of the Lamin B1 genomic binding profile affects rearrangement of heterochromatonic domains and SAHF formation during senescence. *Genes Dev.* 2013, 27, 1800–1808. [CrossRef]

175. Lukasova, E.; Kovarík, A.; Bačiková, A.; Falk, M.; Kozubek, S. Loss of lamin B receptor is necessary to induce cellular senescence. *Biochem. J.* 2017, 474, 281–300. [CrossRef]

176. Boumendil, C.; Hari, P.; Olsen, K.C.F.; Acosta, J.C.; Bickmore, W.A. Nuclear pore density controls heterochromatin reorganization during senescence. *Genes Dev.* 2019, 33, 144–149. [CrossRef]

177. D’Angelo, M.A.; Gomez-Cavazos, J.S.; Mei, A.; Lackner, D.H.; Hetzer, M.W. A change in Nuclear Pore Complex Composition Regulates Cell Differentiation. *Dev. Cell* 2012, 22, 446–458. [CrossRef]

178. Sellés, J.; Penrad-Mobayed, M.; Guillame, C.; Fuger, A.; Auvray, L.; Faklaris, O.; Montel, F. Nuclear pore complex plasticity during developmental process as revealed by super-resolution microscopy. *Sci. Rep.* 2017, 7, 14732. [CrossRef]

179. Gonzalez-Suarez, I.; Gonzalo, S. Nurturing the genome: A-type lamins preserve genomic stability. *Nucleus* 2010, 1, 129–135. [CrossRef]

180. Redwood, A.B.; Gonzalez-Suarez, I.; Gonzalo, S. Regulating the levels of key factors in cell cycle and DNA repair: New pathways revealed by lamins. *Cell Cycle* 2011, 10, 3652–3657. [CrossRef]

181. Moiseeva, O.; Bourdeau, V.; Vernier, M.; Dabauvalle, M.-C.; Ferbeyre, G. Retinoblastoma-independent apoptosis is accompanied by degradation of lamin A+C during apoptosis. *Cell Cycle* 2001, 703–709. [CrossRef]

182. Moiseeva, O.; Bourdeau, V.; Vernier, M.; Dabauvalle, M.-C.; Ferbeyre, G. Retinoblastoma-independent regulation of cell proliferation and senescence by the p53-p21 axis in lamin A/C-depleted cells. *Aging Cell* 2011, 10, 789–797. [CrossRef]

183. Oberhammer, F.A.; Hochegger, K.; Fröschl, G.; Tiefenbacher, R.; Pavelka, M. Chromatin condensation during apoptosis is accompanied by degradation of lamin A+C, without enhanced activation of cdc2 kinase. *J. Cell Biol.* 1994, 126, 827–837. [CrossRef]

184. Slee, E.A.; Adrain, C.; Martin, S.J. Executioner Caspase-3, -6, and -7 Perform Distinct, Non-redundant Roles during the Demolition Phase of Apoptosis. *J. Biol. Chem.* 2001, 276, 7320–7326. [CrossRef] [PubMed]

185. Ruchaud, S.; Korfali, N.; Villa, P.; De Kleijn, A.; Wessels, L.; de Laat, W.; et al. Domains of the nuclear lamina are revealed by mapping of nuclear lamina interactions. *Cell Cycle* 2010, 9, 1341–1348. [CrossRef]

186. Naetar, N.; Korbei, B.; Kozlov, S.; Kerenyi, M.A.; Dorner, D.; Kral, R.; Gotic, I.; Fuchs, P.; Cohen, T.V.; Bittner, R.; et al. Loss of nucleoplasmic LAP2α–lamin A complexes causes erythroid and epidermal progenitor hyperproliferation. *Nat. Cell Biol.* 2008, 10, 1341–1348. [CrossRef]

187. Brachner, A.; Foisner, R. Lamina-associated polypeptide (LAP)2α and other LEM proteins in cancer biology. *Adv. Exp. Med. Biol.* 2014, 773, 143–163.
190. Raman, M.; Chen, W.; Cobb, M.H.; Bakay, M.; Wang, Z.; Melcon, G.; Schiltz, L.; Xuan, J.; Zhao, P.; Sartorelli, V.; Seo, J.; Pegoraro, E.; Angelini, C.; et al. Nuclear envelope dystrophies show a transcriptional fingerprint suggesting disruption of Rb–MyoD pathways in muscle regeneration. *Brain 2006*, 129, 996–1013. [CrossRef]

191. Raman, M.; Chen, W.; Cobb, M.H.; Differential regulation and properties of MAPKs. *Oncogene 2007*, 26, 3100. [CrossRef]

192. McKay, M.M.; Morrison, D.K. Integrating signals from RTKs to ERK/MAPK. *Oncogene 2007*, 26, 3113. [CrossRef] [PubMed]

193. Wagner, E.F.; Nebreda, Á.R. Signal integration by JNK and p38 MAPK pathways in cancer development. *Nat. Rev. Cancer 2009*, 9, 537. [CrossRef]

194. Kyriakis, J.M.; Avruch, J. Mammalian Mitogen-Activated Protein Kinase Signal Transduction Pathways Activated by Stress and Inflammation. *Physiol. Rev. 2001*, 81, 807–869. [CrossRef]

195. Kyriakis, J.M.; Avruch, J. Mammalian MAPK Signal Transduction Pathways Activated by Stress and Inflammation: A 10-Year Update. *Physiol. Rev. 2012*, 92, 689–737. [CrossRef]

196. Plotnikov, A.; Zehorai, E.; Procaccia, S.; Seger, R. The MAPK cascades: Signaling components, nuclear roles and mechanisms of nuclear translocation. *Biochim. Biophys. Acta Mol. Cell Res. 2011*, 1813, 1619–1633. [CrossRef] [PubMed]

197. Ivorra, C.; Kubicek, M.; González, J.M.; Sanz-González, S.M.; Álvarez-Barrientos, A.; O’Connor, J.E.; Burke, B.; Andrés, V. A mechanism of AP-1 suppression through interaction of c-Fos with lamin A/C. *Genes Dev. 2006*, 20, 307–320. [CrossRef] [PubMed]

198. González, J.M.; Navarro-Puche, A.; Casar, B.; Crespo, P.; Andrés, V. Fast regulation of AP-1 activity through interaction of lamin A/C, ERK1/2, and c-Fos at the nuclear envelope. *J. Cell Biol. 2008*, 183, 653–666. [CrossRef]

199. Arimura, T.; Helbling-Leclerc, A.; Massart, C.; Varnous, S.; Niel, F.; Lacene, E.; Fromes, Y.; Toussaint, M.; Mura, A.M.; Kelle, D.I.; et al. Mouse model carrying H222P-Lmna mutation develops muscular dystrophy and dilated cardiomyopathy similar to human striated muscle laminopathies. *Hum. Mol. Genet. 2004*, 14, 155–169. [CrossRef]

200. Jones, J.I.; Clemmons, D.R. Insulin-like growth factors and their binding proteins: Biological actions. *Endocr. Rev. 1995*, 16, 3–34.

201. Cantley, L.C.; Shaw, R.J. Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature 2006*, 441, 424.

202. Bertacchini, J.; Beretti, F.; Cenni, V.; Guida, M.; Gibellini, F.; Mediani, L.; Marin, O.; Maraldi, N.M.; De Pol, A.; Lattanzi, G.; et al. The protein kinase Akt/PKB regulates both prelamin A degradation and Lmna gene expression. *FASEB J. 2013*, 27, 2145–2155. [CrossRef]

203. Cenni, V.; Bertacchini, J.; Beretti, F.; Lattanzi, G.; Bavelloni, A.; Riccio, M.; Ruzzene, M.; Marin, O.; Arrigoni, G.; Parmaik, V.; et al. Lamin A Ser404 Is a nuclear target of akt phosphorylation in C2C12 cells. *J. Proteome Res. 2008*, 7, 4727–4735. [CrossRef]

204. de Sandre-Giovannoli, A.; Bernard, R.; Cau, P.; Navarro, C.; Amiel, J.; Boccaccio, I.; Lyonnet, S.; Stewart, C.L.; Munnich, A.; Le Merrer, M.; et al. Lamin A truncation in Hutchinson-Gilford progeria. *Science 2003*, 300, 2055. [CrossRef] [PubMed]

205. Eriksson, M.; Brown, W.T.; Gordon, L.B.; Glynn, M.W.; Singer, J.; Scott, L.; Erdos, M.R.; Robbins, C.M.; Moses, T.Y.; Berglund, P.; et al. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. *Nature 2003*, 423, 293. [CrossRef]

206. Mounkes, L.C.; Kozlov, S.; Hernandez, L.; Sullivan, T.; Stewart, C.L. A progeroid syndrome in mice is caused by defects in A-type lamins. *Nature 2003*, 423, 298. [CrossRef]

207. Hernandez, L.; Roux, K.J.; Wong, E.S.M.; Mounkes, L.C.; Mutalif, R.; Navasankari, R.; Rai, B.; Cool, S.; Jeong, J.W.; Wang, H.; et al. Functional coupling between the extracellular matrix and nuclear lamina by wnt signaling in progeria. *Dev. Cell 2010*, 19, 413–425. [CrossRef]

208. Perkins, N.D. Integrating cell-signalling pathways with NF-kB and IKK function. *Nat. Rev. Mol. Cell Biol. 2007*, 8, 49. [CrossRef]

209. Osorio, F.G.; Bárbara, C.; Soria-Valles, C.; Ramsay, A.J.; de Carlos, F.; Cobo, J.; Fueyo, A.; Freije, J.M.P.; López-Otín, C. Nuclear lamina defects cause ATM-dependent NF-kB activation and link accelerated aging to a systemic inflammatory response. *Genes Dev. 2012*, 26, 2311–2324. [CrossRef] [PubMed]
210. Markiewicz, E.; Tilgner, K.; Barker, N.; Van De Wetering, M.; Clevers, H.; Dorobek, M.; Hausmanowa-Petrusewicz, I.; Ramaekers, F.C.S.; Broers, J.L.V.; Blankesteijn, W.M.; et al. The inner nuclear membrane protein Emerin regulates β-catenin activity by restricting its accumulation in the nucleus. *Embo J.*, **2006**, 25, 3275–3285. [CrossRef]  
211. Massagué, J. TGFβ signalling in context. *Nat. Rev. Mol. Cell Biol.* **2012**, 13, 616–630. [CrossRef] [PubMed]  
212. Hellemans, J.; Preobrazhenska, O.; Willaert, A.; Debeer, P.; Verdonk, P.C.M.; Costa, T.; Janssens, K.; Menten, B.; Van Roy, N.; Vermeulen, S.J.T.; et al. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. *Nat. Genet.* **2004**, 36, 1213. [CrossRef]  
213. Lin, F.; Morrison, J.M.; Wu, W.; Worman, H.J. MAN1, an integral protein of the inner nuclear membrane, binds Smad2 and Smad3 and antagonizes transforming growth factor-β signaling. *Hum. Mol. Genet.* **2004**, 14, 437–445. [CrossRef]  
214. Pan, D.; Estévez-Salmerón, L.D.; Stroschein, S.L.; Zhu, X.; He, J.; Zhou, S.; Luo, K. The integral inner nuclear membrane protein MAN1 physically interacts with the R-smad proteins to repress signaling by the transforming growth factor-β superfamily of cytokines. *J. Biol. Chem.* **2005**, 280, 15992–16001. [CrossRef]  
215. Rowley, J.D. Identiﬁcation of a translocation with quinacrine ﬂuorescence in a patient with acute leukemia. *Ann. Genet.* **1973**, 16, 109–112.  
216. Parada, L.A.; McQueen, P.G.; Munson, P.J.; Misteli, T. Conservation of relative chromosome positioning in normal and cancer cells. *Curr. Biol.* **2002**, 12, 1692–1697. [CrossRef]  
217. Paddy, M.R.; Belmont, A.S.; Saumweber, H.; Agard, D.A.; Sedat, J.W. Interphase nuclear envelope lamins form a discontinuous network that interacts with only a fraction of the chromatin in the nuclear periphery. *Cell* **1990**, 62, 89–106. [CrossRef]  
218. Belmont, A.S.; Zhai, Y.; Thilenius, A. Lamin B distribution and association with peripheral chromatin revealed by optical sectioning and electron microscopy tomography. *J. Cell Biol.* **1993**, 123, 1671–1685. [PubMed]  
219. Bouvier, D.; Hubert, J.; Seve, A.P.; Bouteille, M. Characterization of lamina-bound chromatin in the nuclear shell isolated from HeLa cells. *Exp. Cell Res.* **1985**, 156, 500–512. [CrossRef]  
220. Kind, J.; Pagie, L.; Ortatbokzyoyn, H.; Boyle, S.; De Vries, S.S.; Janssen, H.; Amendola, M.; Nolen, L.D.; Bickmore, W.A.; Van Steensel, B. Single-cell dynamics of genome-nuclear lamina interactions. *Cell* **2013**, 153, 178–192. [CrossRef]  
221. Minc, E.; Allory, Y.; Worman, H.J.; Courvalin, J.C.; Buendia, B. Localization and phosphorylation of HP1 proteins during the cell cycle in mammalian cells. *Chromosoma* **1999**, 108, 220–234. [CrossRef]  
222. Makatsori, D.; Kourmouli, N.; Polioudaki, H.; Shultz, L.D.; McLean, K.; Theodoropoulos, P.A.; Singh, P.B.; Georgatos, S.D. The inner nuclear membrane protein lamin B receptor forms distinct microdomains and links epigenetically marked chromatin to the nuclear envelope. *J. Biol. Chem.* **2004**, 279, 25567–25573. [CrossRef]  
223. Brown, C.R.; Kennedy, C.J.; Delmar, V.A.; Forbes, D.J.; Silver, P.A. Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes. *Genes Dev.* **2008**, 22, 627–639. [CrossRef]  
224. Zullo, J.M.; Demarco, I.A.; Piqué-Regi, R.; Gaffney, D.J.; Epstein, C.B.; Spooner, C.J.; Superti-Furga, T.R.; Bernstein, B.E.; Pritchard, J.K.; Reddy, K.L.; et al. DNA sequence-dependent compartmentalization and silencing of chromatin at the nuclear lamina. *Cell* **2012**, 149, 1474–1487. [CrossRef] [PubMed]  
225. Chikashige, Y.; Tsutsumi, C.; Yamane, M.; Okamasa, K.; Haraguchi, T.; Hiraoka, Y. Meiotic Proteins Bqt1 and Bqt2 Tether Telomeres to Form the Bouquet Arrangement of Chromosomes. *Cell* **2007**, 129, 15992–16001. [CrossRef]  
226. Alsheimer, M.; Benavente, R.; Hodzic, D.; Schmitt, J.; Hoog, C.; Stewart, C.L. Transmembrane protein Sun2 is involved in tethering mammalian meiotic telomeres to the nuclear envelope. *Proc. Natl. Acad. Sci. USA* **2007**, 104, 7426–7431.  
227. Bupp, J.M.; Martin, A.E.; Stensrud, E.S.; Jaspersen, S.L. Telomere anchoring at the nuclear periphery requires the budding yeast Sad1-UNC-84 domain protein Mps3. *J. Cell Biol.* **2007**, 179, 845–854. [CrossRef]  
228. Conrad, M.N.; Lee, C.-Y.; Wilkerson, J.L.; Dresser, M.E. MPS3 mediates meiotic bouquet formation in Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. USA* **2007**, 104, 8863–8868. [CrossRef]  
229. Hou, H.; Zhou, Z.; Wang, Y.; Wang, J.; Kallgren, S.P.; Kurchuk, T.; Miller, E.A.; Chang, F.; Jia, S. Csil links centromeres to the nuclear envelope for centromere clustering. *J. Cell Biol.* **2012**, 199, 735–744. [CrossRef]  
230. Zuleger, N.; Boyle, S.; Kelly, D.A.; de las Heras, J.I.; Lazou, V.; Korfali, N.; Battrakou, D.G.; Randles, K.N.; Morris, G.E.; Harrison, D.J.; et al. Specific nuclear envelope transmembrane proteins can promote the location of chromosomes to and from the nuclear periphery. *Genome Biol.* **2013**, 14, R14. [CrossRef]
Albi, E.; Viola Magni, M.P. The role of intranuclear lipids. *Biol. Cell* 2004, 96, 657–667. [CrossRef]

Albi, E.; Lazzarini, A.; Lazzarini, R.; Floridi, A.; Damaskopoulou, E.; Curcio, F.; Cataldi, S. Nuclear Lipid Microdomain as Place of Interaction between Sphingomyelin and DNA during Liver Regeneration. *Int. J. Mol. Sci.* 2013, 14, 6529–6541. [CrossRef] [PubMed]

Albi, E.; Villani, M. Nuclear lipid microdomains regulate cell function. *Commun. Integr. Biol.* 2009, 2, 23–24. [CrossRef] [PubMed]

Fernández-García, P.; Rosselló, C.A.; Rodríguez-Lorca, R.; Beteta-Göbel, R.; Fernández-Díaz, J.; Lladó, V.; Busquets, X.; Escrivá, P.V.; Fernández-García, P.; Rosselló, C.A.; et al. The Opposing Contribution of SMS1 and SMS2 to Glioma Progression and Their Value in the Therapeutic Response to 2OHOA. *Cancers* 2019, 11, 88. [CrossRef]

Casares, D.; Escrivá, P.V.; Rosselló, C.A. Membrane Lipid Composition: Effect on Membrane and Organelle Structure, Function and Compartmentalization and Therapeutic Avenues. *Int. J. Mol. Sci.* 2019, 20, 2167. [CrossRef]

Beale, L. Examination of sputum from a case of cancer of the pharynx and the adjacent parts. *Arch Med. Lond.* 1860, 2, 44.

Beale, L.S. *The Microscope in Its Application to Practical Medicine*; Churchill: London, UK, 1858.

Müller, J. *Über den Feineren Bau und die Formen der krankhaften Geschwülste. On the Nature and Structural Characteristics of Cancer, and of Those Morbid Growths which May be Confounded with It*; G. Reimer: Berlin, Germany, 1838.

Papanicolaou, G.N. New cancer diagnosis. In Proceedings of the Third Race Betterment Conference, Battle Creek, MI, USA, 2–6 January 1928.

De Las Heras, J.I.; Schirmer, E.C. The nuclear envelope and cancer: A diagnostic perspective and historical overview. *Adv. Exp. Med. Biol.* 2014, 773, 5–26.

Friedl, P.; Wolf, K.; Lammerding, J. Nuclear mechanics during cell migration. *Curr. Opin. Cell Biol.* 2011, 23, 55–64. [CrossRef]

Wolf, K.; te Lindert, M.; Krause, M.; Alexander, S.; te Riet, J.; Willis, A.L.; Hoffman, R.M.; Figdor, C.G.; Weiss, S.J.; Friedl, P. Physical limits of cell migration: Control by ECM space and nuclear deformation and tuning by proteolysis and traction force. *J. Cell Biol.* 2013, 201, 1069–1084. [CrossRef]

Suresh, S. Biomechanics and biophysics of cancer cells. *Acta Mater.* 2007, 55, 3989–4014. [CrossRef]

Kraning-Rush, C.M.; Califano, J.P.; Reinhart-King, C.A. Cellular traction stresses increase with increasing metastatic potential. *PLoS ONE* 2012, 7, e32572. [CrossRef] [PubMed]

Swift, J.; Ivanovska, I.L.; Buxboim, A.; Harada, T.; Dingal, P.C.D.P.; Pinter, J.; Pajerowski, J.D.; Spinder, K.R.; Shin, J.-W.; Tewari, M.; et al. Nuclear Lamin-A Scales with Tissue Stiffness and Enhances Matrix-Directed Differentiation. *Science* 2013, 341, 1240104. [CrossRef]

Harada, T.; Swift, J.; Irianto, J.; Shin, J.-W.; Spinder, K.R.; Athirasala, A.; Diegmiller, R.; Dingal, P.C.D.P.; Ivanovska, I.L.; Discher, D.E. Nuclear lamin stiffness is a barrier to 3D migration, but softness can limit survival. *J Cell Biol* 2014, 204, 669–682. [CrossRef]

Shin, J.-W.; Spinder, K.R.; Swift, J.; Chasis, J.A.; Mohandas, N.; Discher, D.E. Laminas regulate cell trafficking and lineage maturation of adult human hematopoietic cells. *Proc. Natl. Acad. Sci. USA* 2013, 110, 18892–18897. [CrossRef]

Rowat, A.C.; Jaalouk, D.E.; Zwergner, M.; Ung, W.L.; Eydelnant, I.A.; Olins, D.E.; Olins, A.L.; Herrmann, H.; Weitz, D.A.; Lammerding, J. Nuclear Envelope Composition Determines the Ability of Neutrophil-type Cells to Passage through Micron-scale Constrictions. *J. Biol. Chem.* 2013, 288, 8610–8618. [CrossRef]

Lombardi, M.L.; Jaalouk, D.E.; Shanaan, C.M.; Burke, B.; Roux, K.J.; Lammerding, J. The Interaction between Nesprins and Sun Proteins at the Nuclear Envelope Is Critical for Force Transmission between the Nucleus and Cytoskeleton. *J. Biol. Chem.* 2011, 286, 26743–26753. [CrossRef]

Denais, C.; Lammerding, J. Nuclear mechanics in cancer. *Adv. Exp. Med. Biol.* 2014, 773, 435–470.

Starr, D.A.; Fridolfsson, H.N. Interactions Between Nuclei and the Cytoskeleton Are Mediated by SUN-KASH Nuclear-Envelope Bridges. *Annu. Rev. Cell Dev. Biol.* 2010, 26, 421–444. [CrossRef]

Sosa, B.A.; Kutay, U.; Schwartz, T.U. Structural insights into LINC complexes. *Curr. Opin. Struct. Biol.* 2013, 23, 285–291. [CrossRef]
253. Maniotis, A.J.; Chen, C.S.; Ingber, D.E. Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure. *Proc. Natl. Acad. Sci. USA 1997, 94, 849–854.* [CrossRef]

254. Dahl, K.N.; Ribeiro, A.J.S.; Lammerding, J. Nuclear shape, mechanics, and mechanotransduction. *Circ. Res. 2008, 102, 1307–1318.* [CrossRef]

255. Lammerding, J. Mechanics of the nucleus. *Compr. Physiol. 2011, 1, 783–807.* [PubMed]

256. Osorio, D.S.; Gomes, E.R. Connecting the nucleus to the cytoskeleton for nuclear positioning and cell migration. *Adv. Exp. Med. Biol. 2014, 773, 505–521.* [PubMed]

257. Gomes, E.R.; Jani, S.; Gundersen, G.G. Nuclear movement regulated by Cdc42, MRCK, myosin, and actin flow establishes MTOR polarization in migrating cells. *Cell 2005, 121, 451–463.* [CrossRef]

258. Gundersen, G.G.; Worman, H.J. Nuclear Positioning. *Cell 2013, 152, 1376–1389.* [CrossRef] [PubMed]

259. Luxton, G.W.G.; Gomes, E.R.; Folker, E.S.; Vintinner, E.; Gundersen, G.G. Linear Arrays of Nuclear Envelope Proteins Harness Retrgrade Actin Flow for Nuclear Movement. *Science 2010, 329, 956–959.* [CrossRef] [PubMed]

260. Rios, R.M.; Sanchis, A.; Tassin, A.M.; Fedriani, C.; Bornens, M. GMAP-210 recruits γ-tubulin complexes to cis-Golgi membranes and is required for Golgi ribbon formation. *Cell 2004, 118, 323–335.* [CrossRef]

261. Lindström, L.; Li, T.; Malycheva, D.; Kancharla, A.; Nilsson, H.; Vishnu, N.; Mulder, H.; Johansson, M.; Rosselló, C.A.; Alvarado-Kristensson, M. The GTPase domain of gamma-tubulin is required for normal mitochondrial function and spatial organization. *Commun. Biol. 2018, 1, 37.* [CrossRef]

262. Poirier, K.; Lebrun, N.; Broix, L.; Tian, G.; Saillour, Y.; Boscheron, C.; Parrini, E.; Valence, S.; Pierre, B.S.; Oger, M.; et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat. Genet. 2013, 45, 639.* [CrossRef]

263. Lindström, L.; Alvarado-Kristensson, M. Characterization of gamma-tubulin filaments in mammalian cells. *Biophys. Acta Mol. Cell Res. 2018, 1865, 158–171.*

264. De Keersmaecker, K.; Rocnik, J.L.; Bernad, R.; Lee, B.H.; Leeman, D.; Gielen, O.; Verachtert, H.; Folens, C.; Munck, S.; Marynen, P.; et al. Kinase activation and transformation by NUP214-ABL1 is dependent on the context of the nuclear pore. *Mol. Cell 2008, 31, 134–142.* [CrossRef]

265. Takeda, A.; Sarma, N.J.; Abdul-Nabi, A.M.; Yaseen, N.R. Inhibition of CRM1-mediated nuclear export leading edge of migrating cells is required for cell migration. *Cell 2008, 131, 1025–1039.* [CrossRef]

266. Joseph, J.; Dasso, M. The nucleoporin Nup358 associates with and regulates interphase microtubules. *Febs Lett. 2008, 582, 190–196.* [CrossRef]

267. Murawala, P.; Tripathi, M.M.; Vyas, P.; Salunke, A.; Joseph, J. Nup358 interacts with APC and plays a role in cell polarization. *J. Cell Sci. 2009, 122, 3113–3122.* [CrossRef]

268. Collin, L.; Schlessinger, K.; Hall, A. APC nuclear membrane association and microtubule polarity. *Biol. Cell 2008, 100, 243–252.* [CrossRef]

269. Hubert, T.; Vandekerckhove, J.; Gettemans, J. Exo70-mediated recruitment of nucleoporin Nup62 at the leading edge of migrating cells is required for cell migration. *Traffic Cph. Den. 2009, 10, 1257–1271.* [CrossRef]

270. Gloerich, M.; Vliem, M.J.; Prummel, E.; Meijer, L.A.T.; Rensen, M.G.A.; Rehmann, H.; Bos, J.L. The nucleoporin RanBP2 tethers the cAMP effector Epac1 and inhibits its catalytic activity. *J. Cell Biol. 2011, 193, 1009–1020.* [CrossRef]

271. Liu, C.; Takahashi, M.; Li, Y.; Dillon, T.J.; Kaech, S.; Stork, P.J.S. The interaction of Epac1 and Ran promotes Rap1 activation at the nuclear envelope. *Mol. Cell. Biol. 2010, 30, 3956–3969.* [CrossRef]

272. Hatch, E.M.; Fischer, A.H.; Deerinck, T.J.; Hetzer, M.W. Catastrophic Nuclear Envelope Collapse in Cancer Cell Micronuclei. *Cell 2013, 154, 48–60.* [CrossRef]

273. Crasta, K.; Ganem, N.J.; Dagher, R.; Lantermann, A.B.; Ivanova, E.V.; Pan, Y.; Nezi, L.; Protopopov, A.; Chowdhury, D.; Pellman, D. DNA breaks and chromosome pulverization from errors in mitosis. *Nature 2012, 482, 53–58.* [CrossRef]

274. Vargas, J.D.; Hatch, E.M.; Anderson, D.J.; Hetzer, M.W. Transient nuclear envelope rupturing during interphase in human cancer cells. *Nucleus 2012, 3, 88–100.* [CrossRef]

275. Malhas, A.N.; Vaux, D.J. Nuclear envelope invaginations and cancer. *Adv. Exp. Med. Biol. 2014, 773, 523–535.*

276. Clubb, B.H.; Locke, M. 3T3 cells have nuclear invaginations containing F-actin. *Tissue Cell 1998, 30, 684–691.* [CrossRef]
277. Brandes, D.; Schofield, B.H.; Anton, E. Nuclear mitochondria? *Science* **1965**, *149*, 1373–1374. [CrossRef]

278. Fricker, M.; Hollinshead, M.; White, N.; Vaux, D. Interphase nuclei of many mammalian cell types contain deep, dynamic, tubular membrane-bound invaginations of the nuclear envelope. *J. Cell Biol.* **1997**, *136*, 531–544. [CrossRef]

279. Malhas, A.; Goulbourne, C.; Vaux, D.J. The nucleoplasmic reticulum: Form and function. *Trends Cell Biol.* **2011**, *21*, 362–373. [CrossRef]

280. True, L.D.; Jordan, C.D. The cancer nuclear microenvironment: Interface between light microscopic cytology and molecular phenotype. *J. Cell. Biochem.* **2008**, *104*, 1994–2003. [CrossRef]

281. Fricker, M.; Hollinshead, M.; White, N.; Vaux, D. The convoluted nucleus. *Trends Cell Biol.* **1997**, *7*, 181. [CrossRef]

282. Gupton, S.L.; Collings, D.A.; Allen, N.S. Endoplasmic reticulum targeted GFP reveals ER organization in tobacco NT-1 cells during cell division. *Plant Physiol. Biochem.* **2006**, *44*, 95–105. [CrossRef]

283. Fischer, A.H.; Taysavang, P.; Jihiang, S.M. Nuclear envelope irregularity is induced by RET/PTC during interphase. *Am. J. Pathol.* **2003**, *163*, 1091–1100. [CrossRef]

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).