Mechanics of the Cell Nucleus

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Abstract

Nucleus is a specialized organelle that serves as a control tower of all the cell behavior. While traditional biochemical features of nuclear signaling have been unveiled, many of the physical aspects of nuclear system are still under question. Innovative biophysical studies have recently identified mechano-regulation pathways that turn out to be critical in cell migration, particularly in cancer invasion and metastasis. Moreover, to take a deeper look onto the oncologic relevance of the nucleus, there has been a shift in cell systems. That is, our understanding of nucleus does not stand alone but it is understood by the relationship between cell and its microenvironment in the in vivo-relevant 3D space.

Keywords

Nuclear mechanics · Mechanotransduction · Nuclear lamina · Nuclear envelope · Nucleoskeleton

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3.1 Introduction

Despite decades of research, cancer metastasis still remains an unsolvable process that induces a devastating prognosis. Recent investigations on the biomechanical aspects of tumorigenesis are highlighted to find genetic and biochemical changes associated with cancer progression. Tumor cells are known to alter their own mechanical properties and responses to external physical cues. Thus, the development and metastasis of cancer are closely regulated by mechanical stresses of the nucleus that regulate the gene expression and protein synthesis. This chapter recapitulates the importance of nuclear mechanobiology, whose malfunctioning provokes overall setbacks of cancer progression.

3.2 Nuclear Structure and Property

3.2.1 Nuclear Envelope

Nuclear envelope is divided into three parts: the outer membrane, inner nuclear membrane, and perinuclear membrane. The outer membrane is connected to the endoplasmic reticulum (ER).

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The difference between outer membrane and ER is the existence of ribosomes [1]. Nesprin, an important protein connecting the nuclear envelope and the cytoskeleton in the outer nuclear membrane of mammals, regulates the cellular mechanosensation [2]. The space between outer membrane and inner membrane is called lumen or perinuclear membrane. The outer membrane and the inner membrane converge at the nuclear pore complexes (NPCs) (Fig. 3.1), through which small molecules diffuse. However, molecules that are larger than 40 kDa can diffuse only by signaling [3]. Nucleoporin, essential for aggregation of lamina in late mitosis [4], is a molecular constituent of NPC. It interacts with the lamina [5] and may be involved in its biogenesis [6]. Inner nuclear membrane consists of transmembrane proteins and membrane -associated proteins such as lamina-associated protein (LAP)s, lamin B receptor (LBR), emerin, and SUN proteins. Interaction between the inner nuclear membrane and proteins is known to occur through these proteins [2].

In the nucleus, integral membrane proteins in the inner nuclear membrane connect the cytoplasm to the chromatin. The inner nuclear membrane has, for example, the lamin-binding proteins, having at least one transmembrane domain and lamin-binding domain [7]. Varied biochemical and physical factors are involved in their interaction with different partners, leading to the subsequent deformation of the nuclear structure. Lamin is connected to chromatin lamin-binding proteins and is involved in the regulation of gene expression. Lamin connected to emerin interacts with chromatin and other inner nuclear membrane proteins [8].

Generally round or oval, the nuclear shape reflects the condition of cells, disease, and age [9]. Lamina regulates the nuclear shape, which affects functioning of the nucleus through altering the shape, structure of chromatin, and gene expression. In addition to lamina, changes in the nuclear shape are caused by forces from cytoplasm and by lipid synthesis. Neutrophils have a distinguishable nuclear shape. If neutrophils have LBR mutation, the nuclei are hypolobulated and the cells malfunction [10]. Lobulation is affected by LBR, nuclear lamina proteins, microtubule, and Kugelkern proteins [11]. In drosophila embryos, the nuclear shape changes from spheroid to ellipsoid by Charleston, inner nuclear membrane protein, and microtubules [12].

Nuclear size is also affected by the cell cycle, reaching its maximum size during interphase [13]. Yeast are able to regulate their nuclear volume, although it has no lamin and lamin-associated protein mechanisms. The nuclear volume and shape are dependent on the physical forces, the osmotic pressure, and the hydrostatic pressure [14].

3.2.2 Nuclear Lamina

Located under the inner nuclear membrane, the nuclear lamina is mainly composed of lamin and lamin-associated proteins, which connect the lamina to chromatin, involved in regulating the gene expression [15]. Lamin is an intermediate filament IV and is the main component of lamina [15]. Lamins have a N-terminal end and a C-terminal end [16]. There are two subtypes of lamin: A-type lamin from LMNA splicing and B-type lamin from LMNB1/LMNB2. B-type lamins are expressed in all tissues, have a CAAX box, and attach to the membrane vesicles during the cell cycle. Expression of A-type lamin is observed later during development and is tissue-specific. A-type lamin is soluble during mitosis. Not all A-type lamins have a CAAX box where posttranslational modification occurs [17]. All lamins have isoprenylated and carboxymethylated end. In addition, A-type lamins undergo proteolytic cleavage [18]. After initiation of mitosis, phosphorylation occurs and the lamina gets disassembled. On completion of mitosis, the lamina reassembles with the emerin, lamin B receptor, and lamina-associated proteins (LAP) [19].

Electron microscopy revealed that the lamina from Xenopus oocyte was composed of filaments having similar diameter to the cytoplasmic intermediate filaments and mesh network of intermediate filaments [15]. The mesh network of the nuclear lamina provides supports to nuclear size, load-bearing, and viscoelastic behavior of

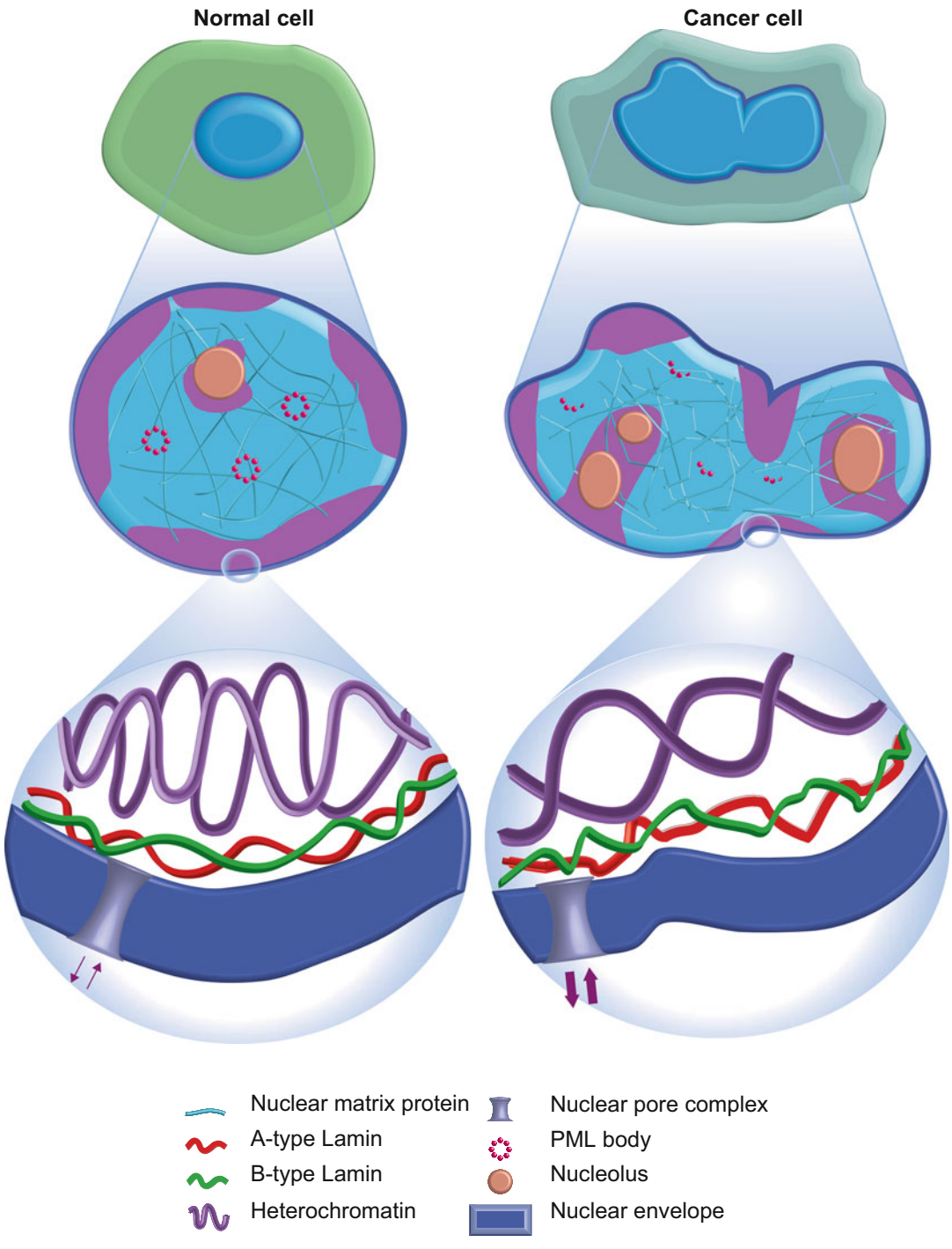

Fig. 3.1 Alteration of nuclear architecture in normal and cancer cells. Cancer cells have lobulated, enlarged, irregular, and folded nuclei. Intranuclear architecture features redistribution of heterochromatin and alteration of structural integrity of lamin proteins. Translocation through nuclear pore complex (NPC) is upregulated, and the formation of PML bodies is inhibited in cancer cells [92]

the nucleus under exterior forces [20, 21]. Nuclei from lamin-Xenopus oocytes, which are bigger than mammals, can be easily manipulated and are observed to be weak [22]. Nuclei from LMNA knockdown mouse cells are deformable [23]. Interestingly, depletion of lamin B does not cause any change in stiffness, but additional blebbing occurs in the nucleus. This implies that lamin A is the dominant factor in controlling nuclear stiffness [24].

Laminopathies are caused by defects of LMNA (Hutchinson-Gilford progeria, cardiopathy, muscular dystrophy) and affect a wide range of tissues. A-type lamin depletion decreases the nuclear stiffness, resulting in enhanced sensitivity to outer stress [24]. Dysregulation in coupling of nucleoskeleton and cytoskeleton and the failure in critical cellular functions such as mechanosensing, differentiation, proliferation, and repairing intracellular damage are the results of diminished lamin proteins [8]. In humans, in particular, autosomal dominant leukodystrophy and adult-onset leukoencephalopathy are associated with disruption of LMNB1 [8]. Since lamin proteins are connected to the chromatin, mutation of lamin could result in malignant cancers as well [8]. The relationship between nuclear lamin and onset of cancer will be discussed more specifically in a later section.

Emerins interact with the inner nuclear membrane, lamin, and chromatin. Emerin-deficient cells show abnormal nuclear shape and mechanotransduction [8]. Several evidences display that microtubule and nuclear envelope are directly connected to each other. In cells which are emerin and A-type lamin-deficient, there is mislocation of MTOC, leading to abnormal cell migration. Interaction between kinesin and nesprin mediates the coupling of microtubule and nucleus. An actin cap is composed of stress fibers on the top of the nucleus, from the apical surface to the bottom. Actin cap is coupled to the nuclear lamina through the LINC complex and nesprins. The actin cap associated with large focal adhesions may be involved in mechanotransduction [25].

3.2.3 Nuclear Chromatin and Associated Proteins in the Nucleus

The building blocks of nucleic acid are nucleotides, which structurally is composed of a nucleoside and phosphate. The DNA double helix combined with histones in the eukaryotic nucleoplasm forms the chromatin, which is organized into chromosomes. Histone H2A, H2B, H3, and H4 are assembled as octamer beads, histone complex [26]. H1, which is not involved in the histone complex, stabilizes the structure. Chromatin is classified as euchromatin and heterochromatin [27]. Heterochromatin is a packed structure, has a low gene expression, and is located on the nuclear lumen or nucleus. Euchromatin is intranuclear, less dense than heterochromatin, and has a high activity of gene expression. Euchromatin has more deformability than heterochromatin, implying that euchromatin is more affected by the extracellular forces [28]. Chromatin untethered to the inner nuclear membrane induces deformable nuclei [29]. Chromatin can deform plastically under fixed stress, influencing the viscosity of the nucleus [30].

Subnuclear structures include the nucleoli, Cajal bodies, and PML. Nucleoli is a fluid-like structure, significantly different from the nucleoplasm [30, 31], having a role in ribosome biogenesis [32]. Cajal bodies are related to the cell cycle. The number and size of Cajal bodies are dependent on the cell cycle, which is maximum at the G1/S phase [33]. PML bodies are responsive to cellular chemical stress. Stressed PML bodies aggregate and achieve posttranslational modification [34].

Other structural proteins present in the nuclear cytoskeleton include nuclear actins, nuclear myosins, and nuclear spectrins. Nuclear actin is not stained with phalloidin because it mainly forms the structure of G-actin and not F-actin [35]. It modulates the gene transcription and chromatin remodeling [36]. Nuclear myosin and spectrin are involved in chromosome movement [37, 38].

3.3 Nuclear Mechanics and Nuclear Mechanotransduction

3.3.1 Intrinsic Mechanics of the Nucleus

Depending on the method of measurement, nuclear stiffness ranges from 0.1 kPa to 10 kPa. Nuclear mechanical properties are largely contributed by the lamina. The proteins associated with lamin compose the lamina and are incorporated into the nuclear membrane and chromatins. Lamina supports the nuclear membrane and renders the stiffness associated with it. Lamina is the mesh network of A-type and B-type lamins; the A-type lamins control the viscosity of lamina, enabling the nucleus to endure applied force [39], whereas the B-type lamins have elasticity which helps restore local deformation [21]. The elastic stiffness of B-type lamin is dependent on the applied force [40]. The ratio of A-type and B-type lamins affects the cellular migration ability [41] and nuclear mechanics.

There are several techniques to measure nuclear properties: micropipette aspiration, AFM, substrate strain, and nuclear microrheology [42]. Measuring the rheology of the nucleus uses the correlation of the applied force and induced deformation of the nucleus [42]. To measure the nucleus, the result is dependent on the condition of nuclei, nuclei in cells or isolated nuclei [42]. In case of measuring nucleus within the cell, the state of nucleus can be preserved physiologically; however, the result is influenced by the cytoskeleton. Measuring isolated nuclei is directly accessible to the probe, but the status of nuclei differs from the living nucleus [42]. Micropipette aspiration is the most widely used technique. Briefly, the nucleus is isolated, or cytochalasin-treated micropipette aspiration directly measures the properties of the nucleus. AFM is used to study adherent cells, providing a high-resolution measurement [42]. However, the results are affected by the environmental factors around the nucleus and are hard to analyze. Substrate strain experiment uses the deformity of the nucleus when cells are stretched by the substrate under the cell. Nuclear microrheology uses inserted magnetic beads to control forces by tweezers [43]. A-type lamin-depleted cells are more easily deformable and enter small pores effortlessly, thus emphasizing that A-type lamin is important for nuclear mechanics.

3.3.2 Cytoskeleton and Nucleus Coupling

Forces from outside the cell are transduced through integrin and cytoskeleton, finally reaching the nucleus through cytoskeleton and nucleus molecular coupling [44]. In this regard, the coupling of nucleus and the cytoskeleton is important for sensing microenvironment and responding mechanically. There are three kinds of cytoskeleton: actin microfilament, microtubule, and intermediate filament. Actin is used to compose protrusions and contractile forces. Intermediate filaments enhance the structure. Microtubule supports the cell shape, motility, mechanical integrity, and division. Hence, these three types of filaments are essential for mediating mechanosensing [28].

The nucleus has a specific complex to interact with exterior forces. The cell is anchored by focal adhesion called the linker of nucleoskeleton and cytoskeleton (LINC). The inner nuclear membrane protein and outer nuclear membrane protein form and connect cytoplasmic and nucleoplasmic skeletons [45]. Nesprins are present on the outer nuclear membrane, connecting with the cytoskeleton in the cytoplasm via actin-binding sites [45]. There are five types of isoforms in nesprin. Nesprin-1 and nesprin-2 are connected to actin filaments in the cytoplasm [46]. Nesprin-3 is connected to the plectin required for cell migration [47]. Nesprin-4 is bound to kinesin-1 positioning MTOC and Golgi complex [48]. KASH domain of nesprin is bound to SUN, which resides in the inner nuclear membrane. In mammals, SUN 1/2 is widely expressed and interacts with A-type lamin. SUN1 connects the lamin A, chromatin, and nesprin 2. SUN2 is involved in vesicle formation and is bound to

lamin, nesprin, and chromatin. SUN3 interacts with nesprin-1 [49]. As emerin stabilizes the lamin, nesprin, and chromatin, the cells with depleted emerin suffer from irregular nuclear shape and lack of mechanotransduction. Increasing evidences suggest a direct connection between the nuclear envelop and microtubules. Emerin and β-tubulin interaction provides an element for centrosomes to attach [50].

LINC establishes the location of nuclear membranes, appropriate positioning, size, anchorage of nucleus, cell migration, and cytoskeletal positioning. Increasing evidence reveals that lamin, especially A-type lamin rather than B-type lamin, plays a critical role in managing mechanotransduction. Depletion of Nesprin-1, SUN-1, or A-type lamin results in synaptic nuclei mislocation, which induces muscular dystrophy [8]. Cells interact with ECM through integrin which consists of FAK, talin, and vinculin. The characteristics of ECM are reflected in the variations seen in cell adhesion, shape, motility, and differentiation properties of cells. The A-type lamin is especially essential for regulating the mechanics of nucleus and cellular mechanotransduction [24].

3.3.3 Nuclear Mechanotransduction

In vivo, cells undergo shear stress, compression, forces during migration, and strain. Nuclear shape changes depending on the transmitted forces from the microenvironment. Nuclear deformation is the rate-limiting step in cell migration through small pores. During migration through collagen, the nucleus can be compressed up to 10% of the initial nuclear size. Alterations in composition of nuclear envelope affects the nuclear shape, inhibits the transmission of forces through the envelope, and finally hinders the cell polarization [51], differentiation [52], migration [53], and proliferation [54].

Vascular endothelial cells suffer from shear stress. Shear stress aligns cells toward the direction of flow. On application of 24 h-shear stress, the nuclei of endothelial cells remodel the cytoskeleton, and nuclear structures flatten, elongate, and become more dense. These changes are stable and persist even after removal of the shear stress [55]. Also, the cells in cartilage or muscle get frequently compressed. In response to the compression force, the nuclear shape, height, and chromatin structure get altered [56]. Chondrocytes lacking the A-type lamins have less stiff nuclei and therefore undergo less resistance, disrupted linkage, and finally isotropic deformation. Wild-type chondrocytes undergo anisotropic deformation [57].

Stretching of tissues can be easily observed *in vivo*. To mimic the stretched tissue, mouse and human fibroblasts were seeded on the silicon membrane, and the silicon substrate was stretched. Nuclei with A-type lamin-deficient cells were deformed at up to 30% of the applied force. The result indicates that depletion of the LINC complex can ruin the deformation of nucleus by strain stress [23]. Substrate patterning and stiffness control the cellular cytoskeletal tension and positioning. The stiffness of the substrate is associated with the magnitude of traction force delivered to the nucleus [58]. Patterning influences cell polarization and nuclear positioning. Cells on micropattern spread and form the axis of the nucleus-centrosome-Golgi [59].

When forces are applied to cells, mechanosensitive proteins react through phosphorylation, modifying the conformation and binding affinity and initiating biochemical signaling. MAPK pathway is one of the major pathways of regulating cellular response to mechanical stresses. Mutation of LMNA elevates the level of phosphorylation of ERK and JNK, causing cardiomyopathy [60]. YAP/TAZ pathway is one of the pathways in the Hippo pathway. YAP/TAZ mediates cellular response to substrate stiffness and tension of the cytoskeleton [61]. A-type lamin overexpression induces decrease in YAP1 levels [39]. MLK1/SRF pathway regulates growth factor, muscle-specific fusion and differentiation, and cytoskeletal dynamics. MLK1/SRF is very sensitive to organization of actin. MLK1 interacts with G-actin and is unable to translocate to the nucleus. This location of MLK1 regulates gene expression [62]. Wnt signaling is critical in bone differentiation upon physical cues. The transcriptional coactivator β-

catenin, which is involved in the Wnt pathway, interacts with nuclear envelope proteins and regulates the sensitivity of osteoblasts or osteocytes to physical stress [63].

3.3.4 Nuclear Mechanoresponse and Chromosomal Reorganization

Epigenetic modification is defined as the regulation of gene expression without altering the DNA sequencing. Chromatin, which is repeated to form nucleosome, is the complex of DNA and core histone proteins [64]. Epigenetic mechanisms include DNA methylation, covalent histone modification, and noncovalent modifications. DNA methylation occurs at CpG-rich dinucleotides, called "CpG islands," which are usually located in the 5′ end of the genes and the promoter [65]. Most of DNA methylations disappear during differentiation and development [66]. However, some CpG islands remain methylated during differentiation and development, which results in long-term effects [67]. Recent studies focus on the role of non-CpG island methylation which occupies 40% of the human gene promoter [65].

DNA methylation hinders the approach of the transcription regulators [68].. DNA methylation in mammals is operated by de novo methyltransferases (DNMT1/DNMT2/DNMT3A/DNMT3B) in normal development and disease [69]. Histone modifications occur at the N-terminal of histone proteins by covalent modification such as methylation, acetylation, and phosphorylation [26]. Changes of histone modifications remain in the form of a histone code, activating or repressing the movement and expression of the chromatin. [27] However, the mechanism of passing down the histone code is not fully identified. Lysine acetylation increases the transcription activity; lysine methylation may activate transcription, depending on the type of residue [26, 70]. In mammals, H3K4me3 increases transcription activity [71], whereas H3K9me3 and H3K27me3 play a converse role [26]. Histone modification is controlled by enzymes, which include histone acetyltransferases (HATs), histone methyltransferases (HMTs), histone deacetylases (HDACs), and histone demethylases (HDMs) [72, 73].

Histone modifications and DNA methylation interact with each other [74]. DNA methyltransferases can be induced due to specific genomic space to promote methylation by some HMTs. HMTs in turn regulate the stability of DNA methyltransferases. DNMT can induce HDACs to achieve gene condensation, which is mediated by MeCP2 [75].

Besides covalent histone modifications, noncovalent nucleosome and histone repositioning regulate the gene expression by changing chromatin organization. Nucleosomes control the accessibility of DNA sequences, altering gene expression by ATP-dependent chromatin remodeling complexes [76]. The nucleosome-free region (NFR), located upstream of the expressed genes, mediates the transcription complex to bind or detach to both ends of genes [77]. Incorporating histone variants, for example, H3.3 and H2A.Z, influences gene expression. Histone variants have a few differences of amino acid from that of normal histone proteins. Activated promoters are occupied by H3.3 and H2A.Z [78]. Histone variants are also modified by acetylation and ubiquitylation, affecting nuclear location and function [79, 80].

miRNAs, which are endogenous ∼22 nt RNAs [81], are a family of small RNAs that cleaves directly specific mRNA, repressing gene expression [82]. RNA polymerase II generates a primary-miRNA (pri-miRNA). Pri-miRNA becomes a hairpin-shaped structure by a Drosha. Pre-miRNA is translocated to cytoplasm and forms short double-stranded miRNA by Dicer. The double-stranded miRNA is disorganized to a single-stranded miRNA. Mature miRNAs are incorporated into the RNA-induced silencing complex (RISC). miRNAs bind to corresponding nucleotides and regulates the expression of the sequence [83]. miRNA can also affect DNA methylation and histone modification mutually by targeting specific enzymes (DNMT and EZH2) [84, 85].

3.3.5 The Role of Nucleus During Cell Migration

The direction of cell migration is related to the nuclear position, which determines cellular polarity [86]. In case of cells migration in the two-dimensional (2D) flat surface, intracellular organelles are placed in the order of leading edge—MTOC—nucleus rear end [87], which is typically observed in the wound healing assay. The monolayered cells on the wound edge are polarized toward the opposite wound edge and formed protrusions to move to the cell-absent space. Cell migration is triggered to collectively migrate by the serum or lysophosphatidic acid (LPA), which activates CDC42 that reorients the nuclear position. As shown in the previous studies where nuclear reorientation is blocked without activation of dynein motors [88], cytoskeletal reorganization is also critical to guide cell migration. Recent studies have identified transmembrane actin-associated nuclear (TAN) line that is bound to nesprin-2 giant at the outer nuclear membrane and plays a critical role in nucleus repositioning for cell migration [89]. The perinuclear actin cap is a well-characterized subset of actin stress fibers that regulates the nuclear shape in a migrating cell. The actin cap is the contractile actomyosin filamentous structure attached to the interphase nucleus by linkers of nucleoskeleton and cytoskeletons (LINC) [25]. Cells typically display an elongated shape in case that the actin cap forms, which also elongates the nuclear shape in parallel to the actin cap fibers [90].

Nucleus-associated proteins and nucleo-cytoskeleton connections therefore could control the cell migration. Depletion of lamin A/C and/or nesprin-1 hinders cell migration because the disruption of nucleus-cytoskeletal connection via outer nuclear membrane proteins inhibits the formation of focal adhesions that promotes cell adhesion and migration [91].

3.4 Nuclear Mechanics in Oncology

3.4.1 Nuclear Structure in Cancer

Nuclear structure of malignant cells is different from that of normal cells (Fig. 3.1). The structure depends on the cancer type and can be a significant parameter for diagnosis. A variety of cancers feature poly-lobulated, irregular, folded, and enlarged nuclear morphology [92]. Morphological alteration of the nucleus can contribute to cancer metastasis and tumorigenesis, where cancer cells undergo severe nuclear deformation and cytoskeletal remodeling to invade neighboring sites. Since the nucleus is stiffer than the cytoskeletons, nuclear deformability becomes a rate-limiting step in cell migration. Thus, the cross-sectional area of the nucleus and its ratio to the size of pores in the matrix could modulate cancer metastasis [93].

Cancer cells undergo nuclear rupture in the confined micro-channels during the metastasis, where nuclear lamina consisting of two types of nuclear lamin proteins is critical to recover the nuclear envelope. Thus incomplete lamin expression induces the frequent nuclear rupture that ultimately influences the location and functionality of nucleoplasmic and cytoplasmic proteins as well as chromatin structure [23, 94].

3.4.2 Nuclear Proteins in Cancer

Increasing evidences suggest that changes of nuclear protein composition are related to characteristics of malignant cancer cells. For examples, nuclear matrix proetin22 (NMP22) and nucleophosmin (B23) are considered as biomarkers of prostate cancer [95, 96]. Nuclear lamin proteins are known to be differently expressed depending

on the type of cancer. A-type lamins are overexpressed in skin cancer and underexpressed in leukemia and lymphomas [97]. The proteins in nucleoplasm are also altered in cancer cells [98]. Based on these findings, pathologists can judge whether or not there is any malignancy of cancer patients.

Changes in the nuclear proteins in cancer induce malfunctioning in cell division, migration, signaling, and gene expression. Overexpressed A-type lamin promotes the reconstruction of cytoskeleton by upregulation of PLS3 (actin binding protein) and downregulation of E-cadherin in colon cancer cells, resulting in increased migration and invasiveness of cancer cells [99]. Underexpressed nucleoporin 153 alters the structure of nuclear lamina, causing decreased cell migration in human breast cancer cells [6]. Lamin B-deficient microdomains (LDMDs) are frequently observed in prostate cancer (CaP) cells, resulting in multi-lobulations of nucleus and RNA polymerase II stall, which also promotes the cellular aggressiveness and motility of CaP cell line [100]. Emerin is suppressed in ovarian cancer. The loss of emerin induces suppression of GATA6, aberrant mitosis, and nuclear deformation [101]. LAP (lamina-associated polypeptide)-2β is overexpressed in cells of rapidly proliferating malignant hematological diseases, but not in chronic malignant hematological diseases. LAP2β-HDAC (histone deacetylase) binding structure modifies the histone structure, enhancing malignancy in lymphocytes [102]. Genetic alterations of nesprin-1 and nesprin-2 were found in breast cancer cells [103]. Nuclear pore protein 88 kDa (NUP88) is a constituent of nuclear pore complex. Overexpression of NUP88 induces the transport of NF-κB between nucleus and cytoplasm in breast cancer, colon cancer, and melanoma. NF-κB is associated with the immune system, apoptosis, and cancer. Accumulation of NUP88 in the nucleus upregulates NF-κB activation, which may cause cells to act malignantly [104].

Nuclear matrix (NM) proteins regulate gene expression, DNA replication, and repair. Recent studies have revealed that the NM proteins are associated with progression of cancers and they can be used as biomarkers, e.g., CvC 1–5 (cervical cancer protein) for cervix cancer marker, BLCA-4 (bladder cancer-specific antigen) for bladder cancer marker, RCCA (renal cell carcinoma antigen) 1–2 for renal cancer marker, NMBC-6 (nuclear matrix breast cancer) for breast cancer marker, and CCSA-3 (colon cancer-specific antigen) for colon cancer marker [96].

3.4.3 Nuclear Epigenetics in Cancer

Changes in nuclear architecture are tightly associated with the epigenetic modification of intranuclear chromosomal organization due to chromatin deformation. DNA methylation plays a role in cancer initiation by hypomethylation and aberrant promoter hypermethylation [105]. DNA hypomethylation is verified by amplification of intermethylated sites (AIMS). AIMS are used to find epigenetic alterations in colorectal cancer [106]. Hypomethylated genes repress apoptosis and promote cell proliferation, making cancer cells malignant [106]. Moreover, DNA hypermethylation in cancer inhibits the expression of tumor suppressor genes, which undergoes site-specific gene silencing and cancer initiation. For instance, CAGE [107] and cyclin D2 [108] in gastric cancer and 14-3-3 [109] in pancreatic cancer are hypomethylated, while hypermethylated BRCA1 causes initiation of breast cancer [110].

Loss of histone acetylation, for example, deacetylated H4-lysine 16 (H4K16ac) and H4-lysine 20 trimethylation (H4K20me3) by HDAC, represses gene expression; HDAC is overexpressed in several cancers. For instance, HDAC1 protein plays a role in proliferation and prostate cancer development [111], and the loss of monoacetylated histone H4 is commonly found in human tumor cells [112]. Histone acetyltransferase (HAT) and HAT-related genes are also rearranged to provoke alterations in cancer [113]. Abnormal histone methylation such as H3K9 hypermethylation and H3K27 hypomethylation promotes aberrant gene

silencing in cancer [114]. For example, enhancer of zeste homolog 2(EZH2) is over-activated in breast and prostate cancer [115] because EZH2 expression leads to malfunctioning in regulating cell cycle [115]. EZH2 is involved in the polycomb complex 2 (PRC2) that interacts with the protein influencing the histone methyltransferase activity. DNA methyltransferases (DNMTs) methylate histone H3 lysine 9 and 27 to induce chromatin silencing [116]. This modification recruits the PRC1 which prolongs the silencing [116].

Nucleosome positioning in cancer cells occurs with DNA methylation and histone modification, which renders the nucleosome at the transcription start site. Nucleosome remodeling and deacetylase compressor complex (NuRD) are involved in abnormal gene silencing in leukemia [117]. The switch/sucrose non-fermentable (SWI-SNF) complex mediating ATP-dependent chromatin remodeling is known to play a key role in cancer development and progression. The subunit of SWI-SNF complexes, hSNF5, acts as a tumor suppressor, where depletion of hSNF5 causes inactivation of p21and p16, the cyclin-dependent kinase (CDK) inhibitors. This dysregulated cell cycle induces malignant behavior in rhabdoid tumor cells [105]. One of the histone variants, H2A.Z, prevents the gene to be methylated and mediates the gene activation and controls cellular proliferation and cancer progression. Thus overexpressed H2A.Z is frequently observed in colorectal cancer and breast cancer cells [118].

In cancer cells, some miRNA control gene expressions. These miRNAs, such as lethal-7 (let-7), regulate the stem cell differentiation and prevent the outbreak of tumor by regulating cell differentiation or apoptosis through interrupting gene expression [119]. But some miRNAs have increased gene expression to promote cell differentiation and tumor-like activity [105]. For instance, miR-125b, miR-145, miR-21, and miR-155 are underexpressed in breast cancer [120], and lung cancer cells have underexpressed let-7 [121] and overexpressed miR-17-92 [122], while miR-143 and miR-145 are underexpressed in colorectal neoplasia [123].

3.4.4 The Role of Nucleus During Metastasis

Overcoming nuclear deformation is necessary for effective cancer metastasis [124]. Cancer cells migrate through tissues away from primary tumor via blood vessel and/or lymphatic systems, which causes attenuation of nuclear structural integrity. In case that the pore is smaller than 10% of nucleus diameter, cell can rarely migrate without matrix remodeling [125], which could induce DNA damage and/or epigenetic modification [126].

Cytoskeletons and cytoplasmic structural proteins bound to the nucleus control cell morphology, polarity, and migration patterns. Myosin II activation regulates nucleus sizing process by making cytoplasmic contractile force and squeezing the nucleus during metastasis [127]. Recently, the combination of molecular biology and pathological inspection has shown that the expression of lamin A/C is different from the type of cancers [128], and cancer cells lacking lamin A/C display softer nuclei to make cells invade tissues more easily [129].

3.5 Remarks

Nucleus is a specialized organelle that serves as a control tower of all the cell behavior. While traditional biochemical features of nuclear signaling have been unveiled, many of physical aspects of nuclear system are still under question. Innovative biophysical studies have recently identified mechano-regulation pathways that turn out to be critical in cell migration, particularly in cancer invasion and metastasis. Moreover, to take a deeper look onto the oncologic relevance of the nucleus, there has been a shift in cell systems. That is, our understanding of the nucleus does not stand alone, but it is understood by the relationship between cell and its microenvironment in the in vivo relevant 3D space. For instance, nuclear positioning is known to be mediated by connection between nuclear envelope and several filaments such as actin filament architec-

ture, particularly by the perinuclear actin cap that is typically identified in 2D planar space. Recently research focuses on the discovery of a 3D version of actin cap, the actomyosin fibers binding to nucleus. Since these nucleus-wrapping actin stress fibers could exert mechanical force to squeeze the nucleus and form the pseudopodial protrusions [130], it is implicated to trigger and regulate cell migration in 3D tissue environment. Moreover, since nuclear lamin A/C is required to form organized actin stress fibers, lamin A/C presenting cells in 3D microenvironment could migrate more persistently and faster in 3D than in 2D. Therefore, selection of proper microsystem is as important as underlying mechanism of nuclear biophysics to fully understand the role of nuclear mechanics in the oncology.

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