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Nuclear Lamins in Cancer

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Abstract—Dysmorphic nuclei are commonly seen in cancers and provide strong motivation for studying in various cancer contexts the main structural proteins of nuclei, the lamins. Past studies have separately demonstrated the importance of microenvironment mechanics to cancer progression, which is extremely interesting because the lamina was recently shown to be mechanosensitive. Here, we review current knowledge relating cancer progression to lamina biophysics and biology. Lamin levels can modulate cancer cell migration in 3D and thereby impact tumor growth, and lamins can also protect or not a cancer cell's genome. In addition, lamins can influence transcriptional regulators (RAR, SRF, YAP/TAZ) as well as chromosome conformation in lamina associated domains. Further investigation of the roles for lamins in cancer and even DNA damage may lead to new therapies or at least to a clearer understanding of lamins as bio-markers in cancer progression.

Keywords—Nuclear lamina, Cancer, DNA damage, Genome instability, Mechanotransduction, Homeostasis, SRF, YAP/TAZ, LADs.

INTRODUCTION

Evolution has likely driven our tissues and organs to fulfill their roles with sustained viability. Mature tissues in particular must resist the mechanical demands of an active life. Our bones, cartilage, skeletal muscle and heart tissues are stiff, making them robust to routine physical exertion such as walking or running, during which they are subjected to high-frequency shocks, stresses and strains. Tissue-level deformations might even be amplified within cells and their nuclei.[35] A close correlation between the amount of fibrous collagen extra-cellular matrix (ECM) components and tissue micro-stiffness was recently discovered for mouse tissues.[79] Surprisingly, we also discovered a systematic positive scaling between tissue elasticity and lamin levels in the nucleoskeleton, which implies a novel role for the lamina as a "mechanostat" that mirrors tissue stiffness—that is, nuclei in stiffer tissues will be stiffer due to higher lamin content. Previous studies have also shown a correlation between matrix stiffness, lamin levels and various transcription factors' activation, suggesting a role of lamins in signaling pathways.[79] Continuity between the ECM, the cytoskeleton network (with which lamins interact *via* the LINC complex) and the chromatin might also provide a direct mechanotransduction bridge for the extracellular environment to alter chromosomes.[59] In addition, our initial report last year of lamina-modulated DNA damage in constricted migration of human cancer-derived cells raises the question of whether 'invasion-mutation' mechanisms contribute to the mutation rates and genomic heterogeneity that are highest in the stiffest tissues.[39]

The lamina is a meshwork of intermediate filament (IF) proteins called lamins that lies inside the nuclear envelope and that interacts with both the chromatin and the cytoskeleton (Fig. 1a). In somatic cells in humans and mice as well as most vertebrates, the major forms of lamin protein are expressed from three genes: lamins A and C are alternative splicing products of the *LMNA* gene (collectively 'A-type' lamins) and lamins B1 and B2 are encoded by *LMNB1* and *LMNB2* genes ('B-type' lamins). The lamins show some commonality in amino acid sequence and share structural features, but they differ in their post-translational modifications. B-type lamins are permanently modified by a membrane-inserting farnesyl group that is cleaved from mature lamin-A.[27,38] Like other IFs, such as keratin and vimentin, the lamins form coiled-coil parallel dimers that assemble into higher-order filamentous structures which fulfill important structural roles.[36]

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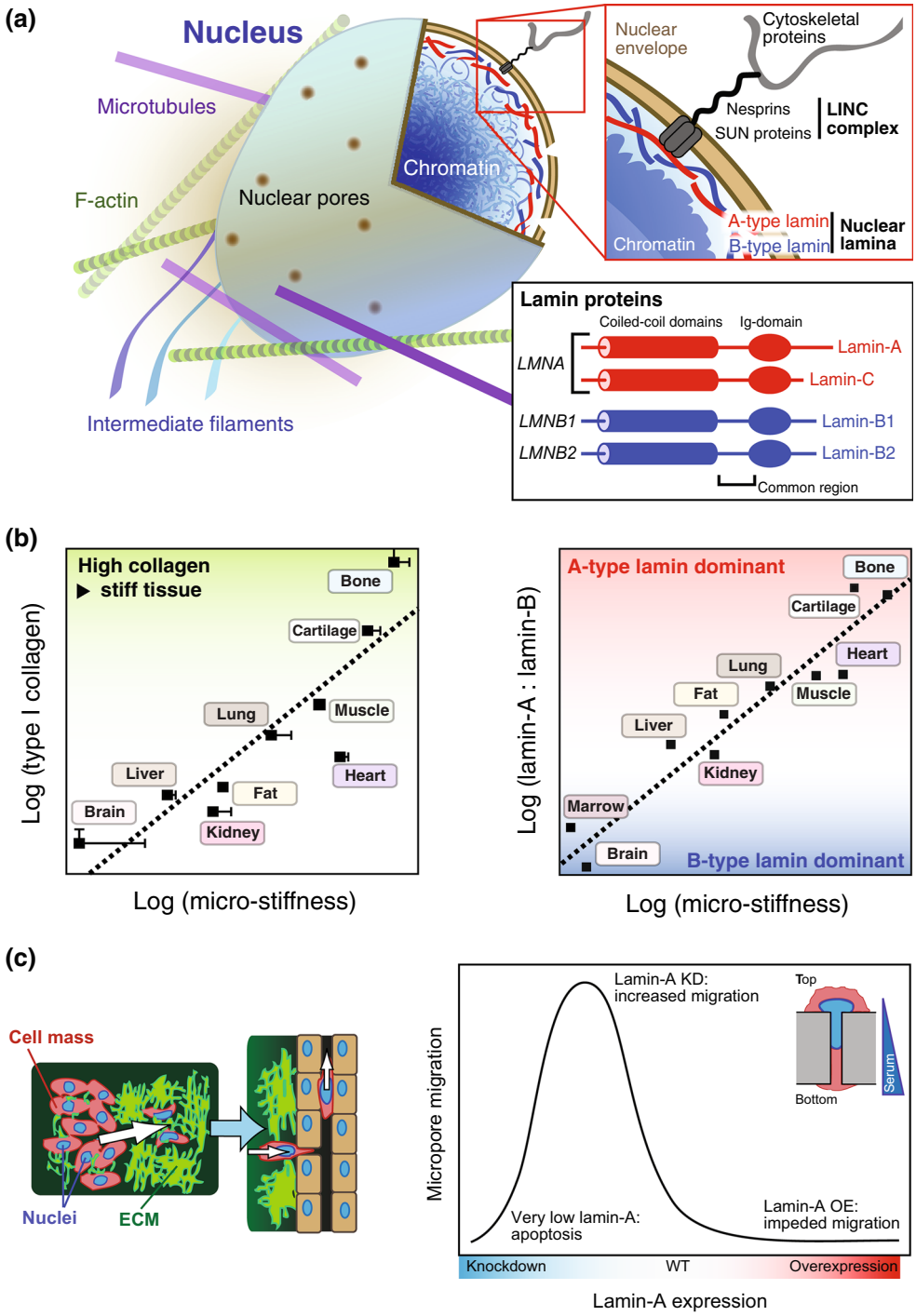

Dysmorphic nuclei are common markers of cancer. Various studies have also demonstrated the influence of a cancer cell's microenvironment in tumor progression, including the effects of niche stiffness that affect cytoskeleton and cell shape. Nuclear shape changes have long been known to correlate with cell shape changes, but relationships to the lamina are just emerging.

THE CANCER LAMINA AND WHAT LITTLE IS KNOWN OF ITS FUNCTION

Evidence from several cancer types as well as from development and aging suggests that nuclear architecture serves as a master integrator for multifactorial microenvironmental signals. Indeed, the microenvironment specifies not just cytoskeletal structure, but

◀FIGURE 1. Nuclear lamin levels scale with matrix stiffness and dictate cancer cell migration potential. (a) A-type and B-type lamins form juxtaposed networks on the inside of the nuclear envelope; they are effectively located at an interface between chromatin and the cytoskeleton, to which the lamina is attached through the 'LINC' (linker of nucleo- and cytoskeleton) complex. 'A-type lamins', lamins A and C are alternative spliceoform products of the *LMNA* gene; 'B-type lamins', lamins B1 and B2 are protein products of *LMNB1* and *LMNB2* respectively (adapted from ©Buxboim *et al.* 2010, originally published in The Journal of Cell Science). (b—left) The quantity of collagen-1 present in tissues scales with tissue micro-stiffness, *E*, and is a main determinant of *E* since collagenase quickly softens and even liquifies tissue.[79] As collagen is one of the most prevalent proteins in the body, it is perhaps expected that it defines mechanical properties. (b—right) The composition of the nuclear lamina also scales with tissue micro-stiffness *E*. A-type lamins dominate the lamina in stiff tissue, whereas B-type lamins are prevalent in soft tissue.[79] (c—left) As the largest and stiffest organelle in the cell, the nucleus can act as an 'anchor', preventing cell movement through the matrix or into surrounding vasculature. (c—right) As a model of migration through matrix, cells are induced to pass through 3 μm-pores, a diameter sufficiently small to require deformation of the nucleus (inset). Lamin-A overexpression inhibits migration, whereas knockdown increases migration, up to a point at which significant apoptosis is observed. Thus extremely low or high lamin-A,C levels are unfavorable for cell migration, an observation with potential impact on understanding of processes such as cell migration during development and cancer metastasis. Importantly, the trends for lamin-A elaborated above for normal tissue reflect an average response but even some intrinsic physiological variation could be selected for in pathology, so that higher or lower lamin levels emerge.

TABLE 1. Lamins in cancer

Type of cancer	Lamin-A,C	Lamin-B
Lung cancer[15]	↓	
Breast cancer[56,87]	↓	↓
Colon cancer[8,56]	↓	↓
Colorectal cancer[3,89]	↑	↑
Colonic and grastic adenocarcinomas[56]	↓	
Primary gastric carcinoma[92]	↓	
Basal cell skin carcinoma[84]	↓	
Skin cancer[82]	↑	
Leukemia[1]	↓	
Ovarian serous cancer[86]	↑	
Ovarian cancer[9,17]	↓	↑
Prostate cancer[23,70]	↓	↑
Liver cancer[78]		↑
Pancreatic cancer[46]		↑

Lamin levels, both lamin-A,C and lamin-B, change in cancers of various organs, suggesting that lamins either play a role in cancer progression or alter in response to it. Adapted from Ref. 28. Arrows indicate decrease (down) or increase (up) of either gene or protein expression.

also nuclear structure[43,45,76,93] and perhaps some aspects of chromosomal state.[35,40,49] Physical signals can thus propagate from the ECM, through adhesions and the cytoskeleton through the LINC complex, and then into the lamina, the nucleus and chromatin, as postulated decades ago.[11,13] In flattened 2D tissues and 2D cultures, the nucleus flattens and orients with cell shape, but the interplay of ECM, adhesions, cytoskeleton, and nucleus in 3D tissues remains understudied. It is now clear that the stiffness of non-condensed, well-hydrated nuclei is controlled by the nuclear lamina, and it is clear that lamin-A,C normally adjusts to the stiffness of 3D tissues, with ECM being a major determinant of tissue stiffness (Fig. 1b). In 2D culture models of soft or stiff matrix, cytoskeleton forces and linkages convey mechanical information from outside-to-inside: both lung cancer and primary mesenchymal stem cells exhibit higher lamin-A,C levels when grown on stiff matrix. Similar results have been found for some human cancer cell lines *in vitro* and in xenografts *in vivo*.[16,20,79] Three-dimensional xenografts of a human glioblastoma line in stiff mouse subcutaneous tissue lead to significantly higher levels of lamin-A,C than xenografts in mouse brain which is soft.[16,79] Further study into mechanisms is needed with 3D systems *in vitro* as well as *in vivo*, which is more relevant to cancers, but trends for 2D and 3D appear consistent thus far. Patterned substrates might be useful for example, but it is clear that *matrix elasticity is upstream of cell shape* since a cell will not spread to fill a large pattern of matrix on a soft substrate. Fibrillar matrices might also be useful,[6] but crosslinking between fibers requires more careful attention because polymer physics tells us that shear rigidity (and Young's modulus, *E*) depends on crosslinking that must percolate in 2D or 3D.

The nuclear envelope mechanically couples the nucleus to the cytoskeleton and to ECM such that the nucleus deforms with the cell.[14,79] Indeed, trans-envelope protein interactions such as SUN-KASH directly link the lamin network to cytoskeletal proteins *via* nuclear envelope spectrin related proteins (nesprins, Fig. 1a).[52,81] When the actin cytoskeleton is cut with laser scissors, the nucleus is observed to move both laterally and away from the culture substratum, demonstrating physical tethering between the cytoskeleton and the nuclear envelope.[51,58] These linkages not only help move the nucleus, but are also a major regulator of cytoplasmic stiffness.[52,79] Embryos are soft as they lack much ECM, and embryonic cells *in vivo* and embryonic stem cells in culture have low lamin-A,C and high levels of the nuclear envelope membrane protein lamin-B receptor (LBR).[71] However, during normal differentiation to mechanically stiff cell types (e.g., muscle, bone), lamin-A becomes predominant, accompanied by changes in LBR and SUN-KASH proteins.[22,60,79] While understanding of the variable expression of these factors—as perhaps co-regulated by mechanical cues[14,79]—is just emerging for normal tissue cells, similar descriptions are emerging more slowly for cancer. Several studies have

shown that lamin levels change in cancers of many organ types when compared to normal tissue (Table 1). One very recent immunohistochemical study of human breast tumors and a few breast cancer cell lines reports global loss of about 80–90% of lamin-A,C, SUN1, SUN2, and nesprin-2.[50] However, it is not yet known whether or why such changes in lamin level are associated with changes in LBR and/or other SUN-KASH proteins. Such coordinated changes could suggest reversion of cancer cells to an embryonic state and/or changes in the coupling of nucleus to cytoskeleton, adhesions, and ECM.

Aging is amongst the highest risk factors for cancer in humans, and so it is intriguing that the only accelerated aging syndromes that affect most human organs and that are currently known in humans involve either DNA repair factors (e.g., Werner Syndrome) or lamin-A,C (e.g., Progeria). Children with such mutations have the striking appearance of octogenarians. Degradation of metabolic pathways is closely associated with aging progression,[7] but mutations in metabolic factors (and other factors implicated in aging) seem less significant to broad phenotype, accelerated aging conditions in humans than the aforementioned DNA repair proteins and lamin-A,C. As expected of mutations in DNA repair, Werner Syndrome increases the risk for multiple types of cancer. On the other hand, it remains unclear whether lamin-A,C contributes to chromatin stability like a DNA repair factor.[41,54,91] Different adult cell types normally express very different amounts of both lamin-A,C and LBR, whereas B-type lamin levels (especially lamin-B2) vary minimally across adult tissue lineages,[79] although such trends have yet to be quantified in aging and Progeria. At the molecular scale, lamin-A,C is more mobile and dynamic than B-type lamins,[66] and Progeria mutants of lamin-A,C, with the farnesylated end intact, behave like B-type lamins.[24] In numerous cancers, both A- and B-type lamins change,[28] but there are no reports that the Progerin form of lamin-A is altered or important despite aging as a risk factor in cancer.

Since lamins are the main structural proteins of nuclei, efforts to document changes in lamin levels in cancers have long been motivated by the dysmorphic nuclei that are a hallmark of cancer—often called "nuclear atypia." In breast cancer, for example, evidence of higher mean levels of lamin-A have been associated with better clinical outcomes.[17,26,87] Culture studies suggest that cells with stiffer nuclei might have greater nuclear integrity,[14,33,79,80] but it is also clear that a stiffer nucleus prevents invasive migration through small micro-pores (3 μm diameter) even though modest changes in lamin-A levels have no effect on migration in 2D nor in migration through large pores.[64,67] In lung cancer, lamin-A levels also tend to be low.[15] Mechanistic studies of one human lung cancer line have shown that such cells in the periphery of 3D dermal xenografts (with similar stiffness as normal lung) exhibit more distended nuclei compared to the tumor core and express lower levels of lamin-A relative to lamin-B.[34] Partial transient knockdown of lamin-A,C also led to threefold more rapid growth of tumors initially, and made nuclei softer by about fourfold while allowing cells to migrate about fourfold more efficiently through small micro-pores (Fig. 1c). Deep knockdown of lamin-A,C in the same studies increased apoptosis only after migration through the small micro-pores, suggesting that DNA damage within a relatively unprotected nucleus during invasion through rigid and constraining microenvironments could be sufficiently high to *initiate* cell death. Inhibition of at least one factor required for DNA repair was indeed found to decrease the number of cells that successfully migrated through micro-pores.[34] These are the first studies to link one hallmark of cancer, 3D migration, to another hallmark of cancer, DNA damage, that can in turn lead to lasting genomics changes which contribute to cancer.

Beyond the reported changes in lamin-A,C, elevated levels of lamin-B1 have also been reported at least in human liver cancer patients.[77] Causes and consequences of all such lamin changes in cancer remain in need of much deeper study. Selection of cancer subpopulations with lower lamin-A levels was already observed with migration through micro-pores.[34]

As for animal models, transgenic mice have thus far provided limited mechanistic insight. For example, in humans, reduced expression of lamin-A,C in late-stage colon cancer patients has been associated with disease recurrence,[8] but in mice, tissue-specific ablation of lamin-A,C in the gastrointestinal (GI) epithelium shows no effect on overall growth, longevity, or morphology.[85] Crossing these mice into another strain of transgenic mice susceptible to cancer-associated GI polyps also produces only a small increase in polyp size. Such lineage-specific engineering is motivated by the fact that tissue-wide knockout of the mouse lamin-A,C gene as well as expression of the accelerated aging Progeria-causing mutation result in early lethality, usually within weeks of birth, with stunted growth of the musculoskeletal system and evident fibrosis in the cardiovascular system, all of which are stiff tissues that normally exhibit high levels of lamin-A,C.[79] Lamin-B knockouts die at birth with small brains (a soft tissue) and defective innervation.[42] Early death of such mice undermines almost any analysis of the role of lamins in mouse carcinogenesis (perhaps also in humans), but a complete, informative, and cancer-probing rescue was achieved with a mosaic mouse engineered to possess 50% of cells with one form of Progeria and 50%

normal cells, achieving a 1:1 ratio that was surprisingly maintained throughout the normal lifespan of the mouse.[25] The mosaic mice exhibited normal susceptibility to carcinogenic agents applied to lung and skin but reduced invasiveness of tumors caused by a mutagenic agent in the upper GI tract. Perhaps the DNA damage from the latter agent enhances invasion-associated death of the Progeria population of cells that should have a higher level of pre-existing DNA damage[57]; this could be consistent with initial conclusions from the above studies of lung cancer cells migrating through rigid 3D pores.[34] Although altered nuclear compliance of Progeria nuclei[23] needs to be considered, the stiff tissues in mosaic mice exhibit less fibrotic ECM than the same tissues in 100% Progeria mice, leading to the conclusion that accelerated aging of 100% Progeria mice is due to such cell-extrinsic factors. Since mice do not fibrose as dramatically as humans and typically display lessened forms of otherwise highly fibrotic diseases in humans (e.g., muscular dystrophies[29]), insights into human diseases from mouse models might be generally limited when ECM is a major contributor. Given the currently limited findings on the role and regulation of the nuclear lamina in cancer, it is evident that further studies are required.

CANCER GENE EXPRESSION REGULATION: TRANSPORT INTO THE NUCLEUS AND CHROMATIN MODULATION

The changing structure of the cytoskeleton and nucleus in response to microenvironmental physical stimuli can in turn regulate accumulation of nuclear actin, transcriptional co-activators YAP and TAZ of the Hippo pathway, and retinoic acid receptor (RAR) transcription factors.[61,73,79] These three pathways have all been implicated in cancer and are likely representative of many other physically regulated pathways.

Nuclear actin modulates a number of cellular functions,[68] including a switch between quiescence and gene transcription in epithelial cells.[72] Lamin-A contains a nuclear actin binding region and interacts with many actin-binding proteins that affect nuclear actin levels,[37] which suggests that lamin-A contributes more globally to regulation of cell activity. Nuclear actin indeed controls nuclear import of megakaryoblastic leukemia 1 (MKL1), which is a co-activator of the transcription factor serum response factor (SRF)[37] and is also a gene associated with acute megakaryocytic leukemia (AML) *via* translocation to a dysfunctional fusion protein. SRF normally regulates its own expression together with many other actin-interacting genes, including vinculin, smooth muscle actin, and nonmuscle myosin-IIA (MYH9), such that knockdown of lamin-A decreases expression of SRF pathway genes more so than any other single pathway.[16,37,79,83] These mechanisms thus regulate a feedback loop between the acto-myosin cytoskeleton and the nuclear lamina. Human breast and melanoma cancer cell lines depleted of MKL1, SRF, or even just myosin-IIA failed to colonize mouse lung from the bloodstream as they were unable to persist after arrival.[53] Increased cancer rates are not reported in humans with heterozygous, weakly dominant negative mutations of MYH9-related diseases that otherwise do cause diseased platelet, kidney and cataract phenotypes.[74] On the other hand, myosin-IIA has also been reported to be a tumor suppressor in a mouse screen for genes involved in skin cancer.[65] Myosin-IIA levels may only become critical when they are very low, facilitating strong feedback effects on SRF and driving cancer. Overall, these findings suggest that low levels of lamin-A might also be accompanied not only by low SUN2, *etc*. per above, but also by low levels of myosin-IIA, affecting cell tension and contributing to nuclear atypia in cancer.

Hippo pathway signaling involving YAP/TAZ is well-known to regulate growth in response to key contributions from cell junctions, polarity, and cytoskeleton[12]; loss of such spatial control is a hallmark of cancer. Increased YAP/TAZ activity has been implicated in the progression of some cancers: for example, YAP is limited to progenitor compartments of normal colon, lung, and ovary tissues, but in tumor tissues there is strong and diffuse nuclear and cytoplasmic YAP expression.[75] In mammary cells, nuclear YAP/TAZ also affects lineage specification[19,69] and mediates contact inhibition *via* the actin cytoskeleton,[5] with up-regulation in breast cancer.[31] Notably, YAP/TAZ activity responds to mechanical stresses involving the ECM-cytoskeleton-lamin interconnectivity. In epithelial sheets in culture, YAP/TAZ activity is regulated by F-actin-capping/severing proteins (Cofilin, CapZ, and Gelsolin), and it is confined to cells exposed to mechanical stress, such as those on the sheet edge or along curved contours.[5] In mesenchymal stem cells (MSCs) in 2D culture on stiff mechanical environments, YAP accumulates to affect differentiation fates even after cells have been transferred to a different mechanical environment.[94] Interestingly, lamin-A,C overexpression actually decreases nuclear YAP in similar culture systems, which is consistent with decreased levels of YAP in a rigid normal tissue such as bone compared to muscle (Fig. 2)[79]; the same set of studies also suggests that some fraction of nuclear YAP localizes specifically near the nuclear lamina, with only one envelope protein (ELYS) identified by mass spectrometry analyses of proteins co-immunoprecipi-

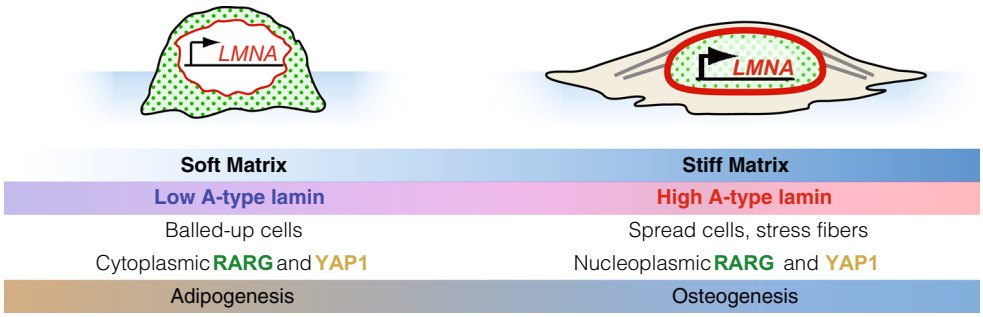

FIGURE 2. Decisions of cell fate downstream of lamin-A,C regulation. MSCs cultured on soft and stiff substrates take on differing phenotypes and favor alternate cell fates.[32] On soft substrate, MSCs exhibit small nuclear and cellular spread areas, and the nuclear lamina is thinned by a stress-sensitive phosphorylation feedback mechanism.[79] The transcription factors RARG and YAP1[31] remain in the cytoplasm, and adipogenic cell fate is preferred. Conversely, on stiff substrate, cells spread extensively with nuclei that are pinned down by well-developed stress fibers. Lamin-A,C is less phosphorylated under strain, thus strengthening the lamina; RARG also translocates to the nucleus, increasing *LMNA* transcription. Activity of the transcription factor SRF (downstream of lamin-A,C) increases expression of cytoskeletal components. Under these conditions, YAP1 translocates to the nucleus and cells favor osteogenesis. On both soft and stiff substrates, the effects of matrix elasticity and lamin level cooperate to enhance differentiation: lamin-A,C knockdown on soft matrix leads to more adipogenesis; lamin-A overexpression on stiff matrix leads to more osteogenesis.

tated with YAP. As for myosin, 3D spheroids of an immortalized retinal pigment epithelial cell line, together with data from a fish model, have recently indicated that YAP contributes to 3D tissue shape and fibronectin assembly, at least partly *via* ARHGAP18-related proteins that activate Rho-GTPase in a manner that cannot be simply rescued by activating myosin-II contractility.[62] Given the frequent parallels between development and cancer, it seems important to now address similar regulatory mechanisms of YAP/TAZ activity or dysfunction in 2D as well as 3D cancer models.

Retinoic acid receptor (RAR) transcription factors have long been known to be mutated in leukemia,[88] but nuclear levels of RARs also regulate diverse developmental pathways, including mammary gland and hematopoiesis.[18,21] Lamin-A,C was one predictable target of RARs, but it was surprising to find that RARG, as one of the three RAR isoforms, forms a feedback loop with lamin-A,C.[79] In at least one line of human lung cancer cells as well as in primary mesenchymal stem cells, rigid matrix was shown to cause cytoskeletal tension and nuclear stress that stabilizes high lamin-A,C (Fig. 2), which helps retain SUN2 at the nuclear envelope; this shift of SUN2 from the endoplasmic reticulum into the nucleus also facilitates RARG entry *via* SUN2-RARG interaction. Such interplay between the nuclear envelope and various microenvironmental factors allows a cell to coordinate signals from physical cues with signals from purely soluble growth factors and cytokines, resulting in altered expression of gene programs by broadly acting transcription factors. Parallels between development and cancer once again motivate a more careful focus on RAR regulatory mechanisms or dysfunction, especially in 3D cancer models.

Beyond the regulated trafficking of transcription-related factors, interactions of chromatin with the nuclear envelope lead to lamina associated domains (LADs) that have a tendency to display histone marks typical of heterochromatin.[55] LADs can influence gene expression[10,44] with up to 1000-fold lower expression than genes located elsewhere in the nucleus of murine ES cells.[2] Cancer stem cells—assuming they exist—are sometimes said to exhibit characteristics of ES cells,[90] and so repression of differentiation state by sequestration into LADs could be an attractive hypothesis for the cancer field to pursue. Indeed, during differentiation of stem cells, genes specific to stem cell function, such as pluripotency genes, move into LADs, while tissue-specific genes tend to move out.[47,63] Likewise, the physical location of the gene locus for the mammary specific milk proteins, whey acidic protein and beta casein, correlate with their activity: when milk proteins are transcribed, the gene is often found at the central edge of its chromosome territory, whereas in hepatocytes, these genes are found in the nuclear periphery.[95]

Despite what might be presumed from the name "lamina associated domain," whether and how lamins influence so-called LADs remains an open question. Indeed, as chromatin tagging methods have improved and as DNA sequencing has become more affordable and extensive, the most recent and complete studies of murine ES cells in culture show that nuclear lamins have surprisingly *zero* role in mediating genome-wide LAD organization in these cells.[4] These latest studies do imply a role for non-lamin nuclear envelope components in genome organization *via* LADs (at least in

ES cells). Artificial tethering of chromatin to the NE can still suppress gene expression.[30,96] Meanwhile, loss of envelope-mediated anchorage of a chromosome in murine cells might increase transcription of genes on that chromosome[48] even if it is confirmed across multiple cell types, including cancer cells in 2D and 3D, that lamins are not major determinants of LADs.

CONCLUSIONS

Cancer cells invariably have an altered genome and so studies of nuclear structure in cancer contexts are well motivated but clearly complicated. We have sought to describe how careful biophysical studies of the lamina shed light on cancer progression. Lamins play a direct role in constraining cancer cell migration and, according to limited mouse models, modulating tumor growth, with lower lamin levels conferring a growth advantage. In addition, the lamina might indirectly affect cancer progression by altering gene expression *via* either transcription factors or changes in chromosomes. These lamin-cancer connections raise numerous possibilities: perhaps the lamina plays a role in epi-genetic modification, leading to oncogene activation, or maybe it acts as a tumor suppressor of sorts by inhibiting migration or by protecting the chromatin from damage that could lead to genomic changes. Our 2015 report of DNA damage in constricted migration of human cancer-derived cells raises the question of whether 'invasion-mutation' mechanisms contribute to the mutation rates and genomic heterogeneity that are highest in the stiffest tissues.[39] Further work is required to elaborate the mechanistic link between lamins and cancer, which may lead to new treatments or at least a clearer understanding of lamins as bio-markers in cancer progression.

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CONFLICT OF INTEREST

Jerome Irianto, Charlotte R. Pfeifer, Irena L. Ivanovska, Joe Swift, and Dennis E. Discher declare that they have no conflicts of interest.

ETHICAL STANDARDS

No human studies were carried out by authors for this article. No animal studies were carried out by authors for this article.

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