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Review

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Nuclear envelope proteins, mechanotransduction, and their contribution to breast cancer progression

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Breast cancer cells frequently exhibit changes in the expression of nuclear envelope (NE) proteins such as lamins and emerin that determine the physical properties of the nucleus and contribute to cellular mechanotransduction. This review explores the emerging interplay between NE proteins, the physical challenges incurred during metastatic progression, and mechanotransduction. Improved insights into the underlying mechanisms may ultimately lead to better prognostic tools and treatment strategies for metastatic breast cancer.

Breast cancer is the most common malignancy for women in the developed world[1] and is estimated to result in over 300,000 new cases and 40,000 deaths in the United States in 2024[2]. Metastasis is a well-established hallmark of breast cancer[3], accounting for over 90% of breast cancer related deaths[4]. Breast cancer metastasis occurs when cancer cells disseminate from a primary tumor and successfully complete the individual steps of the metastatic cascade: acquisition of an invasive phenotype, local invasion, intravasation, survival in circulation, extravasation, and secondary tumor formation[5,6]. Recent studies suggest that fewer than 0.1% of tumor cells successfully complete the metastatic cascade and form secondary tumors[7–9], hinting at the existence of a subpopulation of tumor cells more fit to metastasize[10]. Effective treatments for metastatic cancer remain elusive in part due to the severe inter- and intra-tumor heterogeneity found in breast cancer patients[1]. This heterogeneity is a result of varying molecular subtypes, which reflect the cell type of origin and the acquired mutations, physiological characteristics[1], and tumor microenvironment (TME) interactions[4].

Cancer progression from the initial tumor formation to the emergence of distant metastases is a complex process driven by a series of genetic and cellular alterations that lead to sustained cell proliferation (sometimes interspersed with extended dormancy) and immune evasion[3,7,11]. Although much research has focused on the associated genetic and cellular alterations in cancer cells, these changes alone cannot fully explain cancer progression. It is now widely accepted that additional factors in the TME, such as interaction of cancer cells with stromal cells and their physical environment, must be considered[12,13]. Here, we primarily focus on physical factors, such as mechanical forces and confinement imposed by other cells and the extracellular matrix (ECM), which are increasingly being recognized as playing important roles during all stages of cancer progression[14,15]. In the primary tumor, *solid stress* and increased *hydrostatic pressure* act on the cells within the TME of the primary tumor (see Box 1 for helpful definitions)[14]. During invasion, intravasation, and extravasation, cells experience extensive mechanical stress as they migrate through constrictions often much smaller than the size of the unconfined cells[14,16–18]; in the vascular system, circulating tumor cells (CTCs) experience substantial *fluid shear stress* within the vasculature. To successfully complete metastasis, cancer cells must withstand and adapt to these physical challenges.

Cells sense mechanical stimuli through *mechanotransduction* processes[19,20], in which mechanical forces are converted into biochemical signals that lead to *mechanoresponses* such as increased contractility or changes in gene expression that enable cells to adapt to their physical environment[21]. To date, significant progress has been made in understanding how *mechanosensors* at the cell surface and within the cytoplasm, such as integrins and focal adhesion proteins, contribute to mechanotransduction and mechanoresponses during breast cancer progression. In contrast, the role of the nucleus in this process, and particularly the function of specific NE proteins such as lamins, emerin, SUN proteins, and nesprins, which have all been implicated in cellular mechanotransduction[22], remain to be fully elucidated.

The nucleus plays a pivotal role in mediating the cellular response to mechanical forces; additionally, as the largest and typically stiffest organelle in the cell, the physical properties of the nucleus directly affect the ability of cells to complete several steps of the metastatic cascade[23,24]. For example, the nucleus undergoes substantial deformation as cancer cells pass through narrow spaces during invasion, intravasation, and extravasation[23–26]. Thus, changes in the expression of lamins and emerin, which control nuclear deformability and stability[27–34], could either promote or impair the ability of cells to pass through such confined spaces. Furthermore, extensive nuclear deformation can lead to transient NE rupture, DNA damage, and genomic instability[26,35], which could be detrimental to individual tumor cells, but collectively promote cancer progression by increasing cancer cell heterogeneity.

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Further supporting a crucial role of NE proteins in breast cancer progression, abnormal nuclear morphology, as well as altered expression of lamin A/C, emerin, nesprins, and SUN proteins often correlate with breast cancer progression and patient outcomes[23,25,36–42].

Box 1 | Useful definitions in cellular mechanobiology

Fluid shear stress: The force exerted by fluid flowing parallel to a surface. In tumors, this occurs when interstitial fluid or blood flows over cell layers, acting parallel to the cell surface, and in CTCs suspended within the blood and exposed to fluid shear stress.
Force transmission: The propagation of forces through the cell or ECM. Force transmission requires physically connected structures and is extremely rapid, i.e., occurs nearly instantaneously.
Hydrostatic pressure: The fluid pressure exerted by fluids at rest. In tumors, hydrostatic pressure arises from the accumulation of fluid in the TME, primarily due to leaky vasculature and impaired lymphatic drainage.
Mechanoresponse: Physical, biochemical, or molecular changes in a cell in response to mechanical stimuli. The mechanoresponse includes the immediate result of the mechanotransduction process and downstream consequences.
Mechanosensors: Cellular structures, such as proteins, ion channels, or organelles, that respond to mechanical stimuli (e.g., pressure, tension, shear stress). These structures transduce mechanical inputs such as forces or deformations into biochemical signals to downstream signaling cascades, leading to a mechanoresponse.
Mechanotransduction: The process by which mechanosensors convert mechanical inputs into biochemical signals. Mechanotransduction processes can include opening of stretch-activated ion channels or mechanically induced conformational changes that alter the interaction of proteins or lipid membranes with binding partners, thereby initiating downstream signaling pathways.
Solid stresses: Mechanical force per unit area imposed by solid (as opposed to fluid) components of a material. In tumors, solid stress can result from confinement of the proliferating tumor by the surrounding tissue, or from direct interaction of cells exerting forces on each other and the ECM. This stress can manifest in several forms: tensile stress (e.g., pulling forces that stretch cells); compressive stress (e.g. pushing forces and compression of cells and their nuclei); and shear stress (e.g., forces tangential to a surface).

Although the precise contribution of these NE proteins to metastatic progression in breast cancer and the underlying mechanism of action remain unclear, increasing evidence suggests that these proteins can modulate cancer progression both through their mechanoresponsive roles and by modulating the physical properties of the cell nucleus. In this review, we will discuss the interwoven relationship between mechanical stress, NE proteins, and their role in mechanosensing and mechanoresponses at the various stages of metastatic progression. We will primarily focus on NE proteins known to be dysregulated in breast cancer, particularly lamins, emerin, nesprins, and SUN proteins, and discuss their interaction with other pathways known to be perturbed in breast cancer.

Nuclear envelope proteins in breast cancer

The nuclear envelope

The NE separates the nuclear interior from the cytoplasm (Fig. 1) and has essential structural and regulatory functions. The NE includes the inner and outer nuclear membranes (INM and ONM, respectively), the nuclear lamina, and nuclear pores, along with a large number of nuclear membrane proteins. The nuclear lamina is primarily comprised of filamentous lamin proteins and provides resistance to nuclear deformation. It also contributes to the regular spacing of nuclear pores and the organization of peripheral chromatin[17,43]. Lamin A and lamin C are splice variants encoded by the *LMNA* gene and are often referred to together as lamin A/C, despite having some unique biological roles[44]. Lamins A/C are major components of the nuclear lamina and regulate nuclear mechanics and stability[31], but also interact with chromatin and numerous transcriptional regulators[32]. The Linker of Nucleoskeleton and Cytoskeleton (LINC) complex consists of nesprin proteins at the ONM and SUN domain proteins at the INM (Fig. 1, inset) and is crucial to transmit forces between the cytoskeleton and nuclear interior[45,46]. Nesprins interact with actin filaments, microtubules, and intermediate filaments, either directly or via other proteins, and bind across the nuclear lumen to SUN domain proteins that interact with lamins, emerin, and the nuclear interior. The mechanisms by which cells regulate the interaction of SUN proteins and nesprins, and thus the *force transmission* across the NE, remains incompletely understood[47,48]. In addition to providing a physical connection between the cytoplasm and nuclear interior, nesprins and SUN domain proteins can also directly interact with important signaling molecules, such as α- and β-catenins[49]. Emerin is a nuclear membrane protein that is retained at the INM through its interaction with lamins A/C but can also be found at the ONM[50]. Lamins, emerin, and LINC complex components are important for maintaining the structure, shape, and function of the nucleus, as well as in transmitting both physical forces and biochemical signals between the cytoplasm and the nuclear interior (Table 1)[22,51]. Importantly, force transmission and

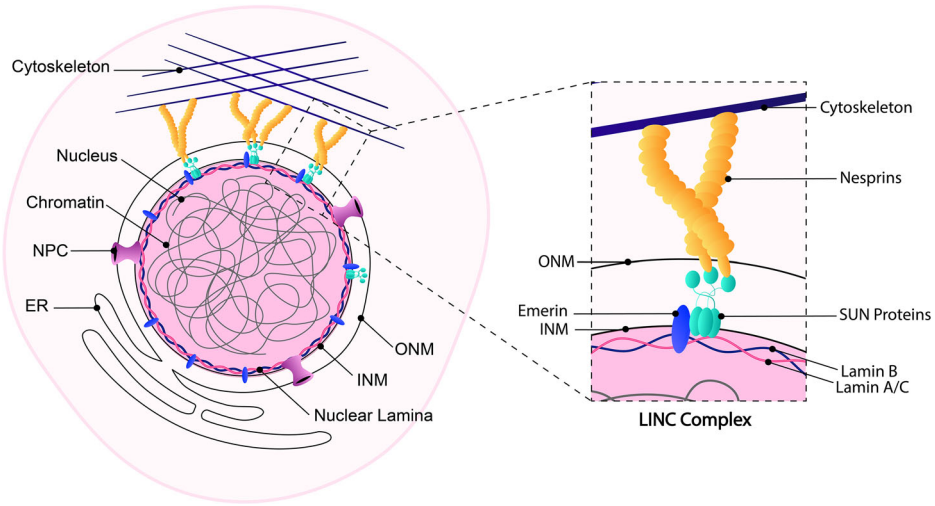

Fig. 1 | Schematic overview of the NE, including the inner nuclear membrane (INM), outer nuclear membrane (ONM), nuclear pore complexes (NPC), and nuclear lamina. The inset on the right shows the LINC complex, comprised of nesprins, SUN domain proteins, lamin A/C and lamin B, and emerin. The LINC complex physically connects the cytoskeleton, including intermediate filaments, microtubules, and F-actin, to the nuclear lamina and the nuclear interior. Together, these components facilitate force transmission between the cytoskeleton and the nucleus and contribute to nuclear mechanotransduction processes.

Table 1 | Overview of key NE proteins discussed in this review

Protein Family	Nesprins	SUN proteins	Emerin	Lamins
Protein Name	Nesprin-1, -2, -3, -4, KASH5 KASH6[48]	SUN1, SUN2, SUN3, SUN4 (only SUN1/2 are expressed in somatic cells)	Emerin	Lamin A, Lamin C, Lamin B1, Lamin B2
Gene Name	SYNE 1-4[151] CCDC155 Jaw1/LRMP[48]	SUN1-3, SPAG4[152]	EMD[30]	LMNA, LMNB1-2[153,154]
Location	ONM[155], although smaller nesprin isoforms can also be found at the INM	INM[152,155]	INM, but also found in the ONM[30,156]	Nuclear lamina, below the INM[154], and nucleoplasm
Background	Mammalian KASH (Klarsicht, ANC-1, Syne Homology) -domain proteins were originally identified as SYNE-1 and -2, but are now commonly referred to as part of the nesprin (Nuclear Envelope SpectRIN repeat proteins[151]) protein family[151,155,157]. Some KASH-domain proteins do not contain spectrin isoforms. Many nesprins have multiple isoforms.	The term "SUN (Sad1 and UNC-84) domain" was introduced following the discovery of a ~ 120-residue motif in the C-terminus of the Caenorhabditis elegans UNC-84 protein. Genome database searches revealed that UNC-84 is evolutionarily conserved, with an increasing number of SUN-domain proteins identified across species[152].	Located on the X-chromosome, consists of six exons, five introns, and encodes a 254 amino acid protein[30]	The nuclear lamina is a dense network of intermediate filaments: A-type lamins, encoded by the LMNA gene, and B-type lamins, encoded by the LMNB1 and LMNB2 genes, are the main constituents of the nuclear lamina[153,154]. Alternative splicing of the LMNA gene results in lamin A and lamin C (lamin A/C)[154].
Common interaction partners at the NE	N-terminal of SUN-domain proteins to form the connection between the cytoskeleton and nucleoskeleton (i.e. the LINC complex)[151,155]	Nesprins-1/2 to form the LINC complex. Nuclear lamina and chromatin to transmit mechanical forces through the LINC complex[51].	Lamin A/C and barrier to autointegration factor (BAF)[30,156].	Emerin, SUN proteins, actin, NUP153, lamina-associated polypeptide 2 isoform alpha (LAP2α)[154], DNA, and various transcriptional regulators.
Function	Nesprins-1/2*: Nuclear positioning[151], nuclear size, shape, and structure[158], chromatin organization[151], and cell migration[158]. Nesprins are important in mechanosignaling through the LINC complex[151,157] and are crucial for transmitting forces from the cytoplasm to the nucleoplasm by interacting with actin filaments, microtubules (via dynein and kinesin), and intermediate filaments (via plectin)[45,151].	SUN1 and SUN2**: Bind to lamins, emerin, nuclear pores, chromatin, and other proteins at the nuclear periphery while directly interacting with KASH domain proteins across the luminal space to connect the nucleus to the cytoskeleton for nucleo-cytoskeletal force transmission and mechanotransduction[152,155,159].	Regulates nuclear signaling, structure, and gene expression[156]	Lamin A/C***: Regulates the structure and mechanics, gene expression, chromatin organization, and DNA replication and repair within the nucleus[154].

*Nesprins-3/4 and KASH5-6 are outside the scope of this review. **SUN3 and SPAG4 are outside the scope of this review. ***B-type lamins are outside the scope of this review

dysregulation of NE proteins such as lamins can alter chromatin organization, including lamin-associated domains (LADs), chromatin accessibility, and epigenetic modifications, along with gene expression and various cellular functions[52–55]. We refer the reader to excellent recent reviews by Dupont et al.[56], Hoskins et al.[54], and Deng et al.[57] on the topic of NE proteins, nuclear force transmission, and chromatin organization and function.

Altered expression of nuclear envelope proteins in breast cancer

Characteristic changes in the nuclear morphology of breast cancer cells, such as size, roundness, presence of invaginations, NE smoothness, and chromatin distribution, are routinely used by clinicians for diagnostic and prognostic purposes, as the increased prevalence of nuclear aberrations in breast cancer cells correlates to worse patient outcomes[36,40,41]. It remains unclear, however, to what extent the observed changes in nuclear morphology result directly from altered expression or function of NE proteins, and if or how such changes mechanistically contribute to breast cancer progression. Supporting a functional involvement, increasing reports indicate that breast cancer tissues exhibit substantial changes in the expression of many NE proteins, and that these changes are associated with disease progression[22]. For example, changes in the expression of nesprin-1/2 have been reported in many cancers, including breast cancer[58,59]. Clinically, the loss of nesprin-2 expression is associated with tumorous tissue regions and correlates to breast cancer invasiveness and intrinsic subtype[39]. Decreased SUN1 and SUN2 expression is observed in tumorous tissue regions, however, their clinical implications are unclear[39]. Invasive breast cancer subtypes have reduced emerin levels and smaller nuclei[29], and overexpression of emerin increases nuclear size, suppresses tumor growth, and reduces lung metastasis in mouse models[29]. Lamin A/C modulate nuclear structure, genomic stability, cell cycle regulation, and response to DNA damage, so it is unsurprising that alterations in lamin A/C lead to aberrations in nuclear morphology[17,33,60], a well-established hallmark to aggressive cancers[3]. Decreased levels of lamin A/C generally correlate with more metastatic cancer cells and worse prognosis in breast cancer patients, whereas higher expression levels are associated with an early clinical stage and better patient outcomes[33,39–42,60,61].

The causes of altered nuclear envelope protein expression in breast cancer

The altered expression levels of NE proteins could arise through multiple mechanisms. The changes are typically not the result of alterations in the copy number of the corresponding gene(s), but are linked to altered transcriptional and epigenetic regulation[62]. For example, hyperactivation of the PI3K/AKT pathway, which is frequently altered in breast cancer, can affect both lamin A/C expression and turnover[61,63,64]. For other NE proteins, the underlying mechanism remains to be determined. It is intriguing to speculate, though, that the altered expression of NE proteins is not only a downstream consequence of oncogenic and tumor suppressor pathways altered in breast cancer cells but might also result from the adaptation of cancer cells to the physical challenges experienced during the metastatic cascade, and/or selection for specific function. In this scenario, the mechanical microenvironment could either activate mechanoresponsive signaling pathways that in turn alter NE protein expression, thereby

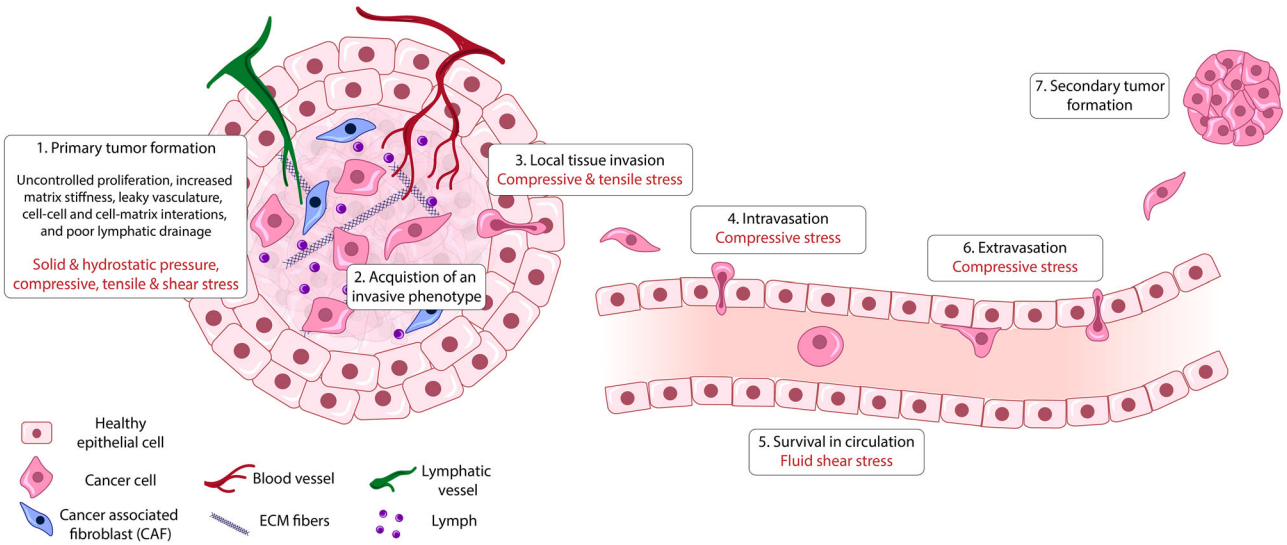

Fig. 2 | Mechanical stress imposed on breast cancer cells from their microenvironment during specific steps of the metastatic cascade. Cells within the primary tumor experience solid and hydrostatic pressure, as well as compressive, tensile and shear stress, imposed by the complex TME. As cell invade the surrounding tissue, they experience compressive and tensile stress. During confined migration events, such as intravasation, and extravasation, cells experience increased compressive stress. In circulation, cell experience increased fluid shear stress imposed by the blood flow.

enabling cancer cells to adapt and enhance their metastatic potential, or the mechanical environment could selectively favor cancer cells with pre-existing elevated or reduced NE protein levels, facilitating their survival through the mechanically challenging environment. Supporting the hypothesis that cells adapt to their microenvironment by altering their NE protein expression, mechanical stimuli can induce numerous changes in the nucleus, affecting nuclear shape, chromatin organization, and expression levels of various NE proteins (reviewed in[65] and[66]). For example, lamin A levels scale with the degree of tissue stiffness[67], and mechanical stress can lead to reduced levels of the SUN domain protein SUN2[68]. Furthermore, mechanical force application promotes phosphorylation of NE proteins, such as emerin[69] and lamin A/C[67,70], affecting their interaction with binding partners and turnover. In the following sections, we will discuss the physical challenges encountered at each stage of the metastatic cascade and explore how changes in the levels of lamins A/C, emerin, and LINC complex components might facilitate cancer cell progression through these stages.

The interplay of nuclear envelope proteins and the mechanical microenvironment during metastatic progression

During tumorigenesis and metastasis, cell behaviors and decision-making processes, such as key cancer hallmarks like migration, proliferation, and apoptosis evasion[3], are modulated by the cell's physical microenvironment[15]. In each step of the metastatic cascade, including primary tumor formation, acquisition of an invasive phenotype, local invasion, intravasation, circulation, extravasation, and colonization, cancer cells are subject to an array of physical forces (Fig. 2). These forces induce mechanoresponses, mediated in part by the nucleus, which enable further cancer progression, and impose selection pressure on the heterogeneous tumor cell population that results in the emergence of cancer cell subpopulations with specific molecular and physical features.

Tumorigenesis

Primary tumor formation is associated with increased cell proliferation and inflammation, as well as growth suppressor evasion and extensive ECM remodeling[3,11]. As a result, cancer cells are subjected to various forces, including compressive and tensile forces, depending on their location within the tumor and the tumor stage[14,20]. Increased solid pressure, from cell proliferation and physical constraints imposed by surrounding cells' ECM, and increased hydrostatic pressure lead to compressive forces. At the same time, cell-cell and cell-ECM interactions are often associated with tensile forces, particularly during the transition to tumor invasion, when cancer associated fibroblasts and immune cells might aid the process by pulling on tumor cells[71,72]. These physical stimuli could promote changes in the expression of NE proteins or conversely lead to selection of cells with altered expression. For example, loss of lamin A/C, and other NE proteins, including nesprin-2, SUN1/2, and emerin, are a signature of tumorous tissue regions[39]. However, severe lamin A/C depletion impairs breast cancer cell spheroid formation in vitro, potentially due to a reduction in transcription levels of the growth regulator Yap1[73]. Taken together, these data indicate that lamin A/C expression may be required for tumor initiation and formation, but lamin A/C depletion may be favorable to tumor progression – suggesting a change in protein expression of the cell population, whether it be through adaptation to mechanical or biochemical cues, survival bias, or a combination of both. Interestingly, lamin A overexpression decreases breast cancer cell proliferation on two dimensional substrates[61], indicating possible competing effects of altered lamin levels during tumorigenesis.

Cell migration: invasion, intravasation, extravasation

A crucial first step in cancer invasion is the acquisition of a migratory phenotype, which can be mediated by an increase in ECM stiffness[74]. Cell migration, both confined and unconfined, is not driven by a single factor, but rather by a complex interplay of both mechanical and biochemical signals. During the subsequent steps, including invasion through the basement membrane and tissues, intravasation, and extravasation, cancer cells must navigate through interstitial spaces and openings in the endothelial cell lining of blood vessels as small as ≈1 μm in size, which is substantially smaller than the 3–15 μm diameter of the nucleus[14,15,22,23,26,61]. Such confined migration involves various intra- and extracellular forces, including actomyosin-mediated traction forces on the ECM and surrounding cells, increased intracellular hydrostatic pressure from cell cortex contraction, cytoskeletal forces pulling on the nucleus, and forces exerted by endothelial cells[17,75–80]. Passing through these small openings places severe mechanical stress on the nucleus, which is approximately 2–10 times stiffer than the cytoplasm[23,26]. As a consequence, the nucleus undergoes large deformation that can lead to transient NE rupture, DNA damage, and increased cell death[34,37,81,82]. Additionally, in vitro studies using microfluidic devices and porous membranes that mimic tight interstitial spaces revealed that confined migration results in altered chromatin organization, including perturbed 3D configuration, chromatin compartmentalization, and

epigenetic modifications[53,83,84]. Even very transient nuclear deformation during perfusion through tight spaces can alter chromatin organization, gene expression, and cell fate[85]. However, it remains unclear whether such changes also occur during transendothelial migration or interstitial invasion in vivo.

It is now well recognized that the deformability of the nucleus constitutes a rate-limiting physical factor in the ability of cells to migrate through confined spaces[17,24,34,86]. Since the deformability of the nucleus is determined by the chromatin in the interior and the composition of the NE, particularly the levels of lamin A/C and emerin[27,28,31,87], changes in the expression of these NE proteins can substantially alter the invasive potential of cancer cells. For example, lower lamin A/C levels result in more deformable nuclei and an enhanced ability of breast cancer cells to migrate through confined spaces[61]. Severe reduction of lamin A/C levels, however, reduces the mechanical stability of the nucleus, resulting in increased NE rupture and cell death in cells migrating through tight spaces[34,37,60,81]. Supporting this multifaceted role of lamins A/C in cancer progression, a recent study found that nearly complete depletion of lamin A/C enhanced cell migration through small rigid pores in vitro, but did not improve transendothelial migration in vivo, and impaired metastasis to the lungs[73]. Reduced emerin levels, which have been reported in various breast cancers[29,88], can similarly increase nuclear deformability and reduce nuclear size, thereby enhancing the invasive potential of breast and prostate cancer cells and promoting metastasis in multiple breast cancer models[29,88,89]. Lastly, NE rupture is determined by nuclear membrane tension[90]. The endoplasmic reticulum (ER) plays a crucial role in regulating and absorbing nuclear membrane tension[91], suggesting that proteins in the ER and NE that control the flow of lipid membrane from the ER to the outer nuclear membrane under tension are key determinants for NE rupture and mechanotransduction.

Besides lamin A/C and emerin, other NE proteins can also contribute to nuclear deformability and changes in invasive potential. For example, depletion of nesprin-1/2 in breast cancer cells results in increased nuclear deformation and degradation of lamin A/C[92]. However, despite the increased nuclear deformability, the cells exhibit a reduced migratory capacity through small pores[92]. Since nesprin-1/2 is an essential component of the LINC complex, nesprin-1/2 depletion might impair force transmission from the cytoskeleton to the nuclei, which could limit the ability of cells to apply sufficient force to the nucleus to move it through confined spaces[76,80]. However, nesprins also play important roles in mechanosensing and in signaling, in part through the WNT/catenin pathway[93–96], which could contribute to the detrimental effects of nesprin-depletion. Further highlighting the often unexpected effects of manipulating NE protein levels, depletion of SUN1 and SUN2 in breast cancer cells, characteristic of the lower SUN1/2 levels found many breast cancer tumors[39,97], increased cancer cell migration along fibers, without affecting migration on 2-D substrates[97]. The effect was mediated by the MKL1-SRF pathway, a key mechanoresponsive signaling pathway that responds to changes in actin polymerization[97]. Another study found that depletion of SUN1, but not SUN2 decreased cell migration through transwell plates with 8-µm-pore filters[98]. The apparent discrepancy between these two studies suggests that the effect of reduced SUN1/2 levels on breast cancer cell motility is context-dependent, with SUN1/2 depletion enhancing movement along fibrous structures but inhibiting migration through three dimensional barriers. Further studies are needed to gain a full understanding of the role of SUN proteins in the migration of cancer cells through physiological environments, and whether these effects are regulated through altered LINC complex mediated force transmission or through other functions of SUN1/2. A recent study on metastatic melanoma cells, which have a high ability to migrate through confined spaces, suggest that cells can use additional strategies to withstand the high physical stress associated with large nuclear deformation incurred during confined migration[99]. The authors found that increased levels of the NE protein lamin-associated polypeptide 1 C (LAP1C) facilitate NE blebbing, which could help reduce stress on the NE and thus avoid damage to the cells during confined migration.

Survival in circulation

In the bloodstream, CTCs experience extreme shear forces from the blood as they traverse the body and anchor to the vessel for extravasation[14,15,20]. Lamin A/C-deficient breast cancer cells, which have more fragile nuclei, show increased cell death under conditions that mimic physiological shear stress levels[100], indicating that adequate levels of lamin A/C are required to protect and maintain the structural integrity of the nucleus in CTCs. These findings align with a recent study showing that shear stress promotes lamin A/C protein accumulation, which modulates the YAP pathway[101]. Given that lamin A/C is a major determinant of nuclear stiffness[31], the accumulation of lamin A/C under shear stress may lead to mechanically more stable nuclei, enabling them to better withstand the shear stress in circulation[100].

Notably, fluid shear stress increases the proliferation, migration, invasive potential, and chemoresistance of cancer cells, including CTCs[101–103], as well as the fraction of cells with a cancer stem cell-like phenotype[104]. These results suggest that cells either adapt and transition into a more invasive phenotype in response to fluid shear stress, or that fluid shear stress acts as a selection pressure, allowing only the most invasive cells to survive. If vulnerabilities in CTCs to survive fluid shear stress can be identified, like a dependence on lamin A/C for survival or the activation of specific pathways, such as YAP, to promote adaptation to shear stress, targeted therapies could be developed to attack these vulnerabilities, hindering CTCs' survival in circulation and preventing cancer cells from reaching secondary sites.

The complexity and dynamics of nuclear envelope dysregulation in breast cancer metastasis

Reduced lamin A/C levels have been shown to both enhance and inhibit metastasis[33,39–42,60,61,73,101,105]. This seemingly paradoxical effect of lamin A/C on breast cancer progression may be explained not only by variations in the location of the tumor samples (e.g., the primary tumor core, the invasive front, or metastatic sites), but also by the diverse functions of lamins, different requirements at each step of the metastatic cascade, and potentially dynamic regulation of lamin levels by metastasizing cancer cells. For example, whereas low lamin A/C levels increase nuclear deformability, which could facilitate invasion, intravasation, and extravasation, complete loss of lamin A/C results in more fragile nuclei that are prone to damage. Additionally, (complete) loss of lamin A/C is expected to also affect other cellular functions modulated by lamins A/C, such as chromatin organization, gene regulation, proliferation etc., which could cause detrimental effects. Thus, cancer cells with an intermediate amount of lamin expression might be best suited to achieve sufficient nuclear deformability to disseminate through the body while ensuring that other functions of lamins critical for metastasis are preserved[61,100].

Furthermore, it is likely that specific stages of cancer progression demand different levels of lamin expression, and by extension, of other NE proteins. For instance, higher lamin A/C levels may be required to maintain nuclear integrity when cell are within the primary tumor, where cells are exposed to compressive stress, or during circulation[100,101,105], whereas invasion, intravasation, and extravasation may favor lower lamin A/C levels and the associated greater nuclear deformability. Yet different lamin A/C levels might be required at metastatic sites to promote metastatic outgrowth and immune invasion.

This raises the question whether cancer cells dynamically regulate lamin expression in response to mechanical cues from their environment, consistent with the concept that the most aggressive cancer cells are highly plastic and adaptable[106–109]. Lamin A/C levels and phosphorylation, which regulates lamin solubility and turnover, respond directly to the mechanical microenvironment[67,70]. Other NE proteins, such as emerin and LINC complex components, are also responsive to mechanical stimuli[68,69,110], raising the intriguing possibility that cancer cells adapt to specific needs during metastatic progression, rather than simply being selected for specific capabilities based on pre-existing properties. In this scenario, mechanical changes of the microenvironment resulting from the uncontrolled cell proliferation within the primary tumor and its interaction with the TME,

which lead to increased solid stress, ECM remodeling, and increased stiffness of the TME[3,14], could further promote cancer progression and invasion, in part through mechanotransduction pathways in the tumor cells and stromal cells. At subsequent steps in the metastatic cascades, the local mechanical microenvironment and the various mechanical forces acting on the cancer cells could trigger additional mechanoresponsive changes that further promote cancer progression. Alternatively, metastatic progression might create a selection pressure, favoring cells with lamin A/C levels low enough to facilitate migration but high enough to withstand the mechanical stress associated with the various steps of metastatic progression. Although currently no experimental data is available to support or refute this hypothesis, such 'mechanical selection' could contribute to the observed low success rate of metastasis[7]. Likely, both adaptation and selection contribute to cancer metastasis, and additional research will be needed to elucidate the specific contributions and the underlying pathways, which could then be explored for therapeutic interventions.

Nuclear mechanoresponse pathways in cancer

The altered expression of NE proteins during breast cancer progression may be driven not only by transcriptional and epigenetic dysregulation but also by mechanoresponses to the physical TME. Several pathways that are known regulators of cancer progression, including PI3K/AKT, TGF-β, ERK/MAPK, YAP/TAZ, have also been implicated in cellular mechanoresponses. Moreover, DNA damage response (DDR) pathways are increasingly being recognized as being part of the cellular mechanoresponse, either following mechanically induced DNA damage or being directly modulated by mechanical stress[35,111,112]. Additionally, activation of these pathways can alter the expression of NE proteins and the mechanical properties of the nucleus[113–117] which could further promoted cancer progression.

PI3K/AKT

One common driver of tumorigenesis and hallmark of invasive cancer is the activation of the PI3K/AKT pathway, typically through oncogenic mutations[118,119]. However, mechanical regulation of the PI3K pathway has become an intriguing focus of research, especially in the context of cancer progression and metastasis. Both increased matrix stiffness and uniaxial compression lead to PI3K/AKT pathway activation in cancer cells, promoting migration, proliferation, and enhanced survival[118,119], and supporting the presence of a mechanoresponsive component to this pathway. NE proteins, particularly lamins, exhibit a bidirectional regulatory relation to the PI3K/AKT pathway[120]. Lamin A overexpression or depletion alters several proteins associated with the PI3K pathway in cancer cells, identifying it as a potential downstream target of lamin A[61,121,122]. Conversely, inhibition of the PI3K/AKT pathway elevates lamin A levels in breast cancer cells, and AKT-positive tumors show reduced lamin A expression[61], suggesting an upstream regulatory role on lamin A expression consistent with previous findings in other cell types[120,123] and underscoring the connection between NE regulation and mechanoresponsive signaling pathways.

TGF-β

TGF-β plays a multifaceted role in breast cancer progression, functioning not only as a cytokine involved in growth, differentiation, and apoptosis but also as a mechanoresponsive signal. TGF-β is upregulated in environments with increased matrix stiffness, inducing epithelial-mesenchymal transition (EMT) via the PI3K/AKT pathway[124,125]. Furthermore, TGF-β-induced EMT is dependent on the spatial distribution of mechanical stress, with more mesenchymal cell phenotypes correlating to regions of increased cytoskeletal tension[126]. Growing evidence suggests that the outcomes of TGF-β stimulation may impact and be impacted by NE proteins – specifically lamin A[62,127]. Treatment with TGF-β increases lamin A phosphorylation in breast cancer cells[127], whereas elevated lamin A expression decreases TGF-β secretion in sarcoma cells[62]. Deletion of SUN2 results in elevated AKT and MAPK signaling, but show a downregulation or unperturbed expression of TGF-β target genes, likely by altered retention of the NE protein MAN1 at the NE, which is a negative regulator of TGF-β signaling[128]. Together, these findings suggest that TGF-β may function in concert with NE proteins and cellular mechanotransduction processes, but the precise role of NE proteins in the TGF-β-mediated mechanoresponse remains to be fully elucidated.

Although TGF-β signaling changes in response to mechanical cues, TGF-β itself might not function as a mechanosensor, and alternative explanations exist. For example, PI3K/AKT might act as the primary mechanoresponse pathway, with TGF-β activation arising from a feedback loop involving PI3K/AKT signaling. Alternatively, the mechanoresponsive effects of matrix stiffness could be mediated through other pathways, independent of TGF-β, resulting in cells becoming more responsive to EMT-inducing signals. Supporting this idea, mechanically activated Piezo2 channels trigger calcium influx, leading to AKT activation and nuclear translocation of the key EMT transcription factor SNAIL[129]. Additionally, inhibition of the NF-κB mechanoresponse pathway suppresses the expression of multiple EMT related transcription factors[130]. Nonetheless, these findings do not rule out the possibility that TGF-β itself is mechanoresponsive. For a detailed discussion of the interplay between TGF-β and NE proteins, we refer the reader to a previous review (Bell et al.[62]).

ERK/MAPK

The ERK/MAPK pathway is a critical signaling cascade involved in cell proliferation, differentiation, migration, stress responses, and survival, with several connections to NE proteins and mechanotransduction processes. Lamin A directly interacts with ERK1/2 in vivo and in vitro[131] and depletion or mutation of lamin A/C leads to perturbed MAPK signaling cascade by hyperactivating the ERK, JNK, and p38α MAPK pathway components[62]. Furthermore, some nesprin-2 isoforms act as scaffolding proteins for ERK1/2, tethering it to the NE[132], and nesprin-1 mutations can increase ERK pathway activation in vitro and in vivo[133]. These findings provide a strong link between the ERK/MAPK pathway and NE proteins. The ERK/MAPK pathway is canonically activated by cytokine and biochemical cues[134], but can also be rapidly activated by mechanical stimulation[135]. Increased matrix stiffness induces an invasive phenotype in breast cancer cells, likely through a mechanoresponsive FAK-Rho-ERK signaling network[136]. Additionally, shear stress induces breast cancer cell proliferation through ERK phosphorylation and nuclear translocation, along with activation of an ERK-YAP signaling cascade[137], although the individual mechanosensitive contributions of ERK versus YAP has not been elucidated.

YAP/TAZ

The YAP/TAZ pathway is a critical mechanoresponsive signaling pathway that integrates cues from substrate stiffness, actin dynamics, and various mechanical stimuli[138,139]. Altered YAP/TAZ signaling has been implicated in many diseases[139–141], including breast cancer[139,141]. In breast cancer cells, shear stress facilitates YAP nuclear translocation[101,137], which promotes lamin A/C protein accumulation[101]. Nuclear compression alone is sufficient to induce nuclear YAP accumulation, in part by opening nuclear pores and facilitating nuclear transport[139,142]. Since lower lamin A/C levels result in more deformable nuclei, reduced lamin A/C expression could also lead to increased YAP nuclear localization in cells subjected to compressive forces. Accordingly, previous studies in Ewing Sarcoma found that lower levels of lamin A levels are associated with increased YAP nuclear localization, enhanced cancer cell migration, and more aggressive disease[143], whereas overexpression of lamin A reduces YAP nuclear recruitment and cell invasiveness[143]. However, whereas lamin A/C increases alongside YAP nuclear translocation in breast cancer cells experiencing shear stress[101], Ewing Sarcoma cells show an inverse relationship, with lower lamin A levels correlating with increased YAP nuclear translocation[143]. These discrepancies may reflect the different mechanical stress applications, cell-type specific differences, or variations in disease-specific mechanisms. A connection between the YAP/TAZ signaling pathway and lamin A/C is supported further by findings in diseases resulting from mutations in the *LMNA* or related genes. For example, muscle stem cells with *LMNA* or nesprin-1

mutations that cause increased nuclear deformability show increased YAP nuclear localization[144], although another study found that muscle cells with a different *LMNA* mutation had impaired nuclear translocation of YAP[140]. Collectively, these findings emphasize the interplay between YAP/TAZ mechanoresponse pathways, NE protein expression, and disease progressions, including breast cancer progression.

DNA damage response pathways

The nuclear lamina plays a crucial role in protecting the contents of the nucleus, maintaining genomic stability, and regulating DDR[145]. Nuclear deformation and NE rupture associated with confined migration or cell compression can cause DNA damage by allowing influx of cytoplasmic nucleases, efflux or exclusion of DNA repair factors, and increasing replication stress[35,146,147], which can be ameliorated at least in part by increased lamin A expression[147,148]. Conversely, DNA damage can trigger NE rupture via ATR kinase pathway activation, leading to lamin A/C phosphorylation, disruption of lamina assembly, and NE rupture[115]. These findings suggest a potential positive feedback loop between low lamin A/C levels and DNA damage, where DNA damage destabilizes the nuclear lamina, exacerbating NE rupture and further reducing lamin A expression. Since lamin A is involved in multiple DNA damage repair pathways, including non-homologous end joining (NHEJ) and homologous recombination (HR), by recruiting repair factors like 53BP1 and BRCA1 to damaged sites[145], loss of lamin A/C might not only increase the risk of DNA damage, but also impair DNA damage repair, which could further drive genomic instability in cancer cells.

Further linking DNA damage and nuclear mechanobiology, several key DDR pathways were recently shown to be responsive to mechanical cues. Ataxia-telangiectasia mutated (ATM) is activated by mechanical stress and directly binds to the cytoskeleton to regulate cell stiffness and migration potential[149]. ATM inhibition leads to stress fiber accumulation, disrupting the normal interplay between the nucleus and cytoskeleton[149]. Interestingly, ATM inhibition also reduces lamin A expression[113], thereby increasing nuclear deformability, suggesting that mutations in the ATM pathways could promote cancer cell invasion by increasing nuclear deformability. Besides ATM, Ataxia-telangiectasia and Rad3-related protein (ATR) also responds to mechanical stress, resulting in ATR recruitment to the NE, independent of DNA damage, to modulate NE plasticity and peripheral chromatin association[112].

Perspectives

As described in the preceding sections, a growing body of evidence indicates an extensive interplay between the physical microenvironment encountered by cancer cells during metastatic progression, cellular mechanotransduction responses, and altered expression of NE proteins that determines the fate of breast cancer cells. However, several key questions remain.

Foremost, it remains unclear whether changes in the expression of NE proteins are driven by adaptation of cells to the physical environment via mechanoresponses[65,66], or if the physical challenges encountered during the individual steps of the metastatic cascade select for a subpopulation of cells from the heterogeneous tumor population that can withstand the increased stress. These possibilities are not mutually exclusive, and it is plausible that a subpopulation of cells is more adaptable to the TME, exhibiting greater plasticity as they traverse the body. These "super-adaptable" cells may further modify their physical and molecular characteristics—such as expression of specific NE protein—in response to the demands of their environment to enhance survival. Alternatively, a subpopulation of tumor cells might exist that is inherently more resistant to mechanical stress within the TME. This "super-fit" population could be selected for as metastasis progresses due to a survival bias based on their NE protein expression. The "super-adaptable" and "super-fit" subpopulations may overlap, forming a subset of cancer cell with the greatest metastatic potential and possibly representing the small fraction of tumor cells that successfully metastasize. Moreover, this "super-adaptable" and "super-fit" subpopulation may overlap with the stem cell-like population frequently associated with disease progression and poor survival. Identifying the specific characteristic signatures of these cells would be highly valuable for prognosis and ultimately for targeting these cells as a therapeutic strategy.

Given the diverse function of NE proteins, it also remains unclear whether the effect of their dysregulation on cancer outcomes is primarily due to their role in cellular mechanosensing and in determining the physical properties of the nucleus, or through more traditional biochemical functions, such as their role in cell signaling or DDR. Similarly, the contribution of genomic alterations versus altered mechanoresponses in driving changes in the expression of NE proteins remains to be fully elucidated, along with the crosstalk between these mechanisms. For example, mechanical stress modulates activation of several mechanoresponse pathways such as YAP and PI3K/AKT[101,137], as well as NE protein expression patterns[101]. Whether these responses are independent of each other or share common upstream pathways will require further investigation. Additionally, when considering perturbed mechanoresponses in cancer cells, it is important to recognize that these changes can arise from at least two separate factors. First, changes in the physical microenvironment, such as stiffening of the stromal environment, can drive pathogenic mechanoresponses that promote a pro-invasive cellular phenotype, even in normal mammary epithelial cells, as demonstrated in a landmark study two decades ago[74]. Second, oncogenic mutations such as the PTEN mutation in the PI3K pathway, and subsequent changes in the expression of other proteins, including NE proteins, can further modulate key mechanotransduction pathways, thereby altering mechanoresponses in cells. Additionally, changes in the physical environment trigger not only acute mechanoresponses but can also influence cellular behavior even after the mechanical perturbation has been removed. This "mechanical memory" is being increasingly recognized as an important factor in metastasis[150], but the precise mechanisms and molecular details underlying mechanical memory formation and retention, which likely involve both epigenetic changes and altered cellular structural organization, remain incompletely understood.

Addressing these questions will require a combination of experimental tools and models to dissect the reciprocal role of mechanical challenges, cellular functions, and NE proteins at each step of the metastatic cascade, going beyond the often still correlative findings shaping our current knowledge. Determining the distinct contributions of cellular adaptation and selection requires time-resolved measurements of specific cellular properties at single-cell resolution, motivating the development of fluorescent reporters for gene expression, chromatin organization, and live-cell biophysical measurements that can be applied in in vivo or ex vivo models mimicking physiological conditions. These experiments should be further aided by more advanced in vitro models that reflect multiple steps of metastatic progression. Current in vitro models typically focus on recapitulating individual steps such as invasion, survival in circulation, or extravasation. Consequently, cells that have been identified as most successful in a particular step, such as confined migration, may ultimately fail in other steps, such as circulation, immune evasion, or metastatic outgrowth. Therefore, developing integrated metastasis models that capture the full metastatic process while preserving the precision and control of in vitro systems could help identify key factors required for successful cancer metastasis. Such models might resolve contradictory findings in the field, such as discrepancies in the contribution of lamin A to breast cancer progression, ultimately providing a more cohesive understanding of NE protein dysregulation in metastasis. Since even the best in vitro models cannot capture all the nuances and complexities of human cancer, it will be crucial to supplement these models with (humanized) in vivo models and analysis of patient tissues, ideally comparing samples from the primary tumor and metastatic sites. These analyses will benefit from spatially resolved -omics approaches to link observed changes to particular physical conditions or subpopulations of cells. Insights gained from these experiments have the potential to improve our understanding of fundamental biological processes, shed light onto the many ways cancer cells adapt to successfully metastasize, and to ultimately uncover novel therapeutic targets to lead to more effective treatment strategies.

Data Availability

No datasets were generated or analysed during the current study.

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S.H. and J.L. conceptualized the discussions in the review. S.H. wrote the manuscript and created the figures. J.L. provided critical feedback and editing. S.H. and J.L. have read and approved this manuscript.

Competing interests

The authors declare no competing interests.

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