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Cancer cell migration in 3D tissue: Negotiating space by proteolysis and nuclear deformability

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Efficient tumor cell invasion into the surrounding desmoplastic stroma is a hallmark of cancer progression and involves the navigation through available small tissue spaces existent within the dense stromal network. Such navigation includes the reciprocal adaptation of the moving tumor cell, including the nucleus as largest and stiffest organelle, to pre-existent or de-novo generated extracellular matrix (ECM) gaps, pores and trails within stromal compartments. Within the context of migration, we briefly summarize physiological and tumor-related changes in ECM geometries as well as tissue proteolysis. We then focus on mechanisms that ensure the successful translocation of a nucleus through a confining pore by cytoskeleton-mediated coupling, as well as regulators of cell and nuclear deformability such as chromatin organization and nuclear lamina expression. In summary, understanding dynamic nuclear mechanics during migration in response to confined space will add to a better conceptual appreciation of cancer invasion and progression.

Space Negotiation in Cancer Cell Migration

Cell migration in vertebrates plays an essential role during embryonic development after which most body cells become resident. An exception form for example leukocytes involved in immune surveillance. In principle, cells have the capacity to reactivate their migratory capacity when required, for example during tissue regeneration, but also in a number of pathologies, such as in cancer. After cancerous transformation, neoplastic cells follow a step-wise cascade that contributes to disease progression.1,2 Cancer cells that undergo an epithelial-to-mesenchymal transition process escape their primary location by basement membrane penetration and detachment from a cell collective by complete or partial downregulation of cell-cell junctional molecules resulting in the formation of small cell groups or single cells.3 The concomitant onset of invasion through tumor-related densified and remodeled connective tissues contributes to hematicogenous or lymphogenous dissemination for subsequent distant metastasis formation and eventually fatal outcome.

The mechanistic process of cell movement that underlies invasion was originally studied over smooth surfaces and consists of a number of consecutive steps (steps 1, 2, 4, and 5 in Fig. 1A).4 These steps, when repetitively carried out, result in forward locomotion of the cell body, which includes the co-locomotion of the nucleus as largest and stiffest cargo in a cell.

These basic requirements for forward locomotion can be adapted or receive additional ‘input’ dependent on specific molecular or physical cellular or environmental determinants. Important examples are spatial extracellular matrix (ECM) organizations, which include both a guidance or barrier function for the forward locomoting cell. When space is sparse, moving cells negotiate for physical space by either removing constricting fibers by focalized proteolysis, or adapting their shape to the pre-existing, only slightly bendable, fibrillar ECM network. ‘Focalized ECM fiber cleavage’ was previously established as an additional migration step in dense environments that follows initial contractile forward pulling to advance the cell body. Tissue proteolysis typically applies to mesenchymal cell types like fibroblasts during wound healing processes or aggressively moving tumor cells. Migratory cell shape adaptation in response to limited space is another established principle in migration. It applies for cells migrating through dense tissue structures in the absence of tissue proteolysis, like tumor cells after blocking of proteolysis. Shape changes also apply to fast moving antigen-scanning immune cells by actomyosin contractility-mediated cell and nuclear deformation.5-7,9 We therefore here extend the concept on proteolytic cell-matrix interaction by the term “space negotiation”, which includes cell-derived proteolytic ECM remodeling, shape change of the cell, and deformation of the tissue (Fig. 1A). In conjunction, the negotiation of the migrating cell for physical space consists of 2 extreme states (Fig. 1B).

One state, depicted at top, represents the sufficiency of physical space for barrier-free migration together with the lack of deformation of the co-migrating nucleus (Fig. 2A and B). The other state, depicted at bottom, represents sparse space combined with the incapability of ECM degradation which forces the moving cell into compensatory amoeboid shape adaptation. Here, cell body and nucleus deform to adapt to and pass through tissue gaps smaller than the cell’s original cross-section (Fig. 2C).7 Between both states, a combination of space generation mechanisms and deformation occurs in a graded fashion, preferentially at lower proteolytic rates, in highly confining matrix geometries, or upon fast migration with incomplete contact-dependent fiber
breakdown. Thus, physical space negotiation during cell migration is the reciprocal interplay of using existing or generated space devoid of solid ECM structure and the pliability of the cell, in particular the nucleus. In this review we will discuss mechanisms of space negotiation, starting with a short summary on components that dictate space availability and then focus on cell morphology-based adaptation mechanisms. Space availability is determined by the (1) ECM geometries and matrix proteolysis, whereas space adaptation involves cellular mechanisms to (2) translocate a nucleus through constricting space for migration, together with (3) components for nuclear deformability and (4) consequences for migration in confined space. The principles of space negotiation also apply to other cell types, in particular leukocytes during immune surveillance. The leukocytes pass through narrow pores imposed by vessel walls and connective tissues and show remarkable abilities to adapt to pre-given tissue structures by nuclear deformations. In this review, however we remain focused on tumor cells and refer the reader to other work highlighting mechanisms of immune cell migration.6,7,9,10,11

### Physical 3D ECM geometries for cell migration

The physical ECM scaffold geometry of stromal connective tissues derives from a number of chemical and physical components. These include density and crosslink status of fibrillar proteins, like collagen and elastin, which determines specific physical fiber organization, alignment, as well as overall and local stiffness values. This results in heterogeneous geometry of ECM-free spaces of least resistance, referred to as gaps, pores and trails that may provide guidance as well as constraints to cells, depending on the tissue region.12-14 In dermal connective tissues, 3D random loose ECM networks of the upper dermis layer merge into aligned packed bundles in the deep dermis, whereas in sub-dermis regions fibers intersperse between fat cells and muscle layers.14,15

During cancer progression, stromal cells like fibroblasts or macrophages become ‘activated’ which often leads to reorganization of the matrix that surrounds the proliferating tumor mass, together with a fibroblast-mediated increase of ECM density and stiffness.16-18 This results in further enhanced physico-chemical ECM heterogeneity with altered anatomical pore spacing, including small trails and clefts that newly appear between stiffened and straightened ECM fibrils. Even though ECM-invading cells may transiently deform or slightly widen compliant fibrils by actomyosin-mediated pushing, the resulting ECM structures provide confined spacing to forward moving cell bodies.19 In consequence, cancer cells employ a number of strategies to ‘negotiate’ limited ECM space.

### Contact-dependent proteolysis of ECM constrictions

ECM degradation can be executed by different enzyme classes, such as matrix metalloproteinases (MMPs), but also cathepsins, or serine proteases.20-25 These enzymes, besides having many other pro-migratory substrates, degrade ECM by different modes of proteolysis, such as intracellular, diffusive or cell-surface associated.21,22,24 ECM contact-dependent proteolysis executes the controlled degradation of ECM polymers that touch and constrict the cell surface. Example cell surface-associated proteases are MMP-2 bound to αvβ3 integrins, the urokinase plasminogen activator type (uPA), or membrane-tethered (MT) cell surface proteases, like the matrix metalloproteinase MT1-MMP, in conjunction with β1 integrins.20,22,27 Cell surface associated proteolysis results in the generation of a de novo ECM-free path that matches the cross section of the forward moving cell.7,26,27 Noteworthy, increased stroma stiffness leads to enhanced cell contractility and elevated MMP activity which correlates with enhanced invasion of surrounding tissue structures.28 However, when tumors of low ECM degradation capability are surrounded by high ECM density, successful tumor migration requires in addition the morphological adaptation of the cell body to the narrow constrictions provided by the matrix.
Cellular and nuclear deformability

Cells are endowed with the capacity to adapt to extracellular tissue structures, an essential function for the build-up and maintenance of healthy tissues. Examples are thin peripheral nerve cone extensions along solid structures such as vessels or myofibers, or morphological adaptation of collagen-producing fibroblasts within the highly ordered tissue structures of tendons.\(^{25,30}\) Within the cell, the soft cytosol has the highest ability to adapt, whereas the nucleus contains 2–10 times higher stiffness (=deformability, elasticity) values.\(^ {31,32}\) Nuclear elasticities derive from a number of determinants that include (1) the level of chromatin compaction as well as (3) the composition of the nuclear lamina in the nucleus. It is speculated that intranuclear actin forms a nuclear scaffold together with chromatin and lamins that contributes to nuclear stiffness.\(^ {33,34}\) Stiffness levels of nucleus and cytoplasm are highly interdependent and, together, are determined by tissue type and differentiation stage of the organism. For example, stiffness levels are lowest in fat, medium in connective tissue, and highest in bone.\(^ {35,36}\) In addition, cellular and in particular nuclear elasticities increase from fetal development into adulthood, and often decrease during transformation from healthy quiescent to neoplastic proliferating tissue.\(^ {37,38}\) Taken together, as a general principle the nucleus remains a relatively stiff and large organelle, which has implications for the forward migration of cells.

Consequences of space negotiation on migration efficacy

The available space determines if and to what extent adaptation by cell and nuclear deformation is required, which together influence migration efficacy (Fig. 1B; Table 1).\(^ {7,12}\) Physical space availability is defined by a combination of intrinsic matrix geometry, matrix deformability defined by stiffness and compliance, as well as by the capacity of the migrating cell to generate proteolytic \textit{de novo} tracks within the matrix.\(^ {7,19}\) For proteolytic migration, this combination maintains migration in all porosities, with highest migration efficacy at optimal pore size. Here, proteases degrade peripheral ECM the mesenchymal cell is “touching”. In increasing ECM densities, pore degradation together with minor deformation of the otherwise ellipsoid nucleus occur, leading to some decrease, but no abrogation, of migration rates. Of note, at oversized pores migration rates decrease again and proteases degrade surrounding matrix only as a ‘bystander effect’.\(^ {12}\) In the absence of proteolysis, oversized and optimal pore sizes maintain migration rates, whereas in confined spaces migration is somewhat reduced as compared to proteolytic migration, but compensated by cellular and nuclear adaptation, referred to as amoeboid deformation (Fig. 2C).\(^ {7,22}\) Very small pore size leads to the abrogation of migration, when the original cross-section of the nucleus is reduced by 90% or more due to proteolysis.\(^ {7,19}\) For proteolytic and non-proteolytic migration depend on net matrix-free space in a bi-phasic manner, where migration is highest at pore sizes that optimally fit the locomoting cell body and decline at mesh sizes that either exceed or limit the cell body. However, in substrate pores that confine or limit the cell, non-proteolytic migration rates decline much faster (Table 1).\(^ {7,39}\) Generally, for migration in confined space, intact
integrin-mediated adhesion coupled to actin contractility (here termed 'mechanocoupling') is crucial and, if disturbed, will lead to early abrogation of migration (Table 1, see column 'Migration efficacy'). Thus, successful migration despite limited space depends on intact mechanocoupling, together with significant deformability of the nucleus.7 In summary, space negotiation for efficient migration depends on (1) net ECM density, together with (2) translocation of the nucleus by actomyosin contractility coupled to ECM adhesion except for leukocytes and (3) the capability of the nucleus for deformation.

### Nuclear Translocation for Migration

Cell movement over a surface requires the basic ‘ingredients’ that consist of cell polarity, protrusion, adhesion, contractility and retraction processes that, when in tune, mediate the forward migration of cell and consequently the nucleus.4,40 Cell migration through 3-dimensional networks of limited space in addition requires the ability of the cell to transport the rigid nucleus against matrix-induced resistance (Fig. 3 [1]). A successful translocation in general, but even more so when tight space must be negotiated, requires the coordinated application of cell-intrinsic forces for (a) proper positioning, (b) anterior pulling and posterior pushing (Fig. 3 [2]), respectively, together with (c) the active deformation of the nucleus. These functions depend fully or in part on the direct connection of the cytoskeletal components to the nucleus via the linker of nucleoskeleton and cytoskeleton (LINC) complex. The LINC complex consists of SUN protein trimers that bind to KASH-domain containing proteins, such as nesprins.41 SUN proteins anchor in the nuclear lamina that underlies the double nuclear membranes designated as ‘nuclear envelope’, whereas nesprins bind, either directly or via further linker proteins, to actin, microtubuli and intermediate filaments (Fig. 3 [3]).5,42

Nuclear re-orientation and positioning processes within the cell take place prior to but also during migration. Initial backward nuclear movement is mediated by microtubules and actomyosin, which together orient and position the nucleus during cell polarization.43,44 Actomyosin-based movements result from special LINC complex organizational structures, transmembrane actin-associated nuclear (TAN) lines that directly link the nucleus to the actin cytoskeleton. Consistently, the absence of SUN proteins or lamin A disturbs the LINC-cytoskeleton axis and thus nuclear positioning for efficient migration.45-46 Future experiments should...
demonstrate whether nuclear positioning is elementary for migration through restricted space.

Next, at the onset of migration, integrins located at the protruding leading edge bind to anterior matrix fibers, and together with concomitant Rho/ROCK-mediated actomyosin coupling and contraction, generate the necessary force to pull the nucleus forward.47,48 Whereas actomyosin-mediated anterior pulling forces require the presence of the LINC complex connection to the nucleus, myosin II activity-mediated posterior nuclear ‘pushing’ by physical force is in principle sufficient to transport the nucleus forward (reviewed in42). The importance of overall actomyosin contractility for nuclear deformation along with forward movement of both cancer- and immune cells through 3-dimensional confined space has been demonstrated after ROCK or myosin II inhibition.7,9 After myosin II inhibition the deformation of nuclei together with the forward locomotion of dendritic cells through dense collagen matrix was abrogated.9

Finally, transport of the nucleus through confined space includes the adaptation of nuclear shape, which might be thought of as a passive process for the dragged nucleus. However, mechanisms that actively deform the nucleus may help cells to transmigrate confining pores and might be essential for forward locomotion in 3D confined ECM matrices. On a stiff glass surface, deformation and flattening of the nucleus occurs by ‘perinuclear actin caps’.49 This highly contractile structure is located basally and apically of the nucleus thereby confining and actively deforming it.48,50 Further, intermediate filaments, such as vimentin, trap nuclei in a cage-like structure and mediate the re-shaping of the nucleus in response to externally applied or actomyosin-generated forces.51 Within a dense constriction, these cytoskeletal structures are implicated in tightly ‘wrapping’ around the nucleus to help the cell to translocate through narrow constrictions. Like TAN lines, the actin cap, as well as intermediate filaments, are physically connected to the nucleus by the LINC complex. Consequently, LINC complex disruption disorganizes nucleo-cytoskeletal-related nuclear deformation and leads to impaired migration.49,52

In conclusion, cytoskeleton-mediated orientation, pulling/pushing, as well as active deformation of the nucleus support the co-locomotion of this rigid organelle during cell migration over surfaces, and presumably through confining space. The effort for active deformation of the nucleus might vary considerably, based on its intrinsic organization and resulting rigidity.

**Components and Regulators of Nuclear Deformability**

The rigidity, or deformability, of a cell nucleus as an important spatial determinant in migration is primarily mediated by (1) chromatin as well as nucleoskeletal organization and (2) expression and assembly of lamins as part of the nuclear lamina. We here summarize the structure of these mediators, with a focus on chromatin and lamins, together with their regulation, especially by ECM stiffness.

**Mediators of nuclear rigidity and integrity**

The organization of *nuclear chromatin* largely determines the size of the nucleus as well as the stiffness of the nuclear interior.53-55 Chromatin organization underlies a dynamic process that includes chromatin doubling from G1 to G2 cell cycle phase, or transcription-related euchromatin/heterochromatin ratios that depend on the developmental, functional or diseased cell stage.56,57 Chromatin decompaction from hetero- toward euchromatin is mediated by histone acetylation where histone acetyltransferases catalyze the addition of an acetyl group that reduces the affinity between histones and DNA.58 This induces increased transcription activity by enhanced accessibility for RNA polymerase and transcription factors.59,60 Chromatin decondensation therefore leads to nuclear size increase as well as nuclear softening.53,55 This was experimentally demonstrated...
after pharmacological inhibition by histone deacetylase inhibitor trichostatin A by micropipette aspiration and atomic force microscopy-mediated nuclear indentation.53,61

Vice versa, chromatin compaction from eu- toward heterochromatin is mediated by histone de-acetylation or histone methylation.56,63 De-acetylation removes a negatively charged acetyl group from a lysine residue within the N-terminal tail of the histone, which enhances the affinity of the histone and the DNA, thereby increasing compaction. Likewise, histone methylation by the methylase inhibitor 5-deoxy-5’-methylthiodenosine, as well as the addition of divalent cations to cells, implies chromatin condensation and is associated with nuclear stiffening.37,63 In conclusion, chromatin organization and compaction reduce size, but increase stiffness of the nucleus.

The nuclear lamina as part of the nuclear envelope fulfills a major role in maintaining the stability and integrity of the nucleus, and is further involved in anchoring and positioning, sizing, shaping and stiffening of the nucleus.65,67 To fulfill these plethora of functions, the lamina forms a structure that envelopes the entire nucleus, as well as part of the intranuclear skeleton, and consists of a dense fibrillar network of type V-intermediate filaments, the lamins. The lamina associates with membrane proteins, such as emerin, lamin B receptor (LBR), SUN proteins, lamin associated polypeptide 1 and 2 (LAP1, LAP2), barrier to autointegration factor (BAF), nurim, otefin, and MAN1.58-70 This organization allows specific interactions with neighboring cellular components, the cytoskeleton to the outside, and chromatin to the inside (Fig. 3 [3]).5,71,72 Whereas, as outlined before, lamina interactions to the cytoskeleton are mediated by the LINC complex, interactions with chromatin are mediated by direct and indirect associations. These involve heterochromatic structures that are located at the nuclear periphery, the lamin-associated domains (LADs), as well as chromatin interactions within the intranuclear skeleton.3,74 Direct lamin-chromatin associations were shown for the B-type lamin Dm0 in Drosophila, and involve the lamin B evolutionary conserved nuclear localization sequence (NLS) domain and the TRAT amino acid sequences with the N- and C-terminal tail domains of core histones.62,75 Indirect lamin-chromatin interactions are mediated by lamin-associated emerin and LAP proteins, where emerin is involved in mechanotransduction and LAP2 α maintains gene-poor and transcriptionally silent structures of heterochromatin.76,77 Thus, the lamina plays an important role to regulate chromatin dynamics and organization.

The lamins, as part of the nuclear lamina, are separated into A- and B-type and contain 7 different lamin protein members, which are encoded by 3 distinct lamin genes in the human genome. Whereas A-type lamins are a splicing variant of one transcript (lamin A, C, C2, AA10) from the LMNA gene located at chromosome 1q21.1–21.3, B-type lamins derive from 2 distinct genes: LMNB1 (lamin B1) located at chromosome 5q23.3-q31.1, and LMNB2 (lamin B1 and B3) present on chromosome 19p13.3. The expression of the lamin subtypes is dependent on cell type and differentiation state and changes between embryonic development, adulthood and cancer. During development, proliferating soft stem cells express B-type lamins, in particular B2, but lack A-type lamins.78 During cell differentiation, A-type lamins are upregulated, which correlates with increased nuclear stiffness, consistent with an increase of the lamin A:B stoichiometry.36,79 An exception is formed by polymorphonuclear neutrophils (PMN’s), which further decrease their already low lamin A/ C levels during further maturation.80 Concomitantly, PMN’s upregulate lamin B receptor for the increase of nuclear membrane surface area, which together causes the formation of soft and lobulated nuclei.81,82 Consequently, mature neutrophilic cell nuclei contain a high pliability and small cross-section, which allows rapid vessel- and tissue transmigration for the performance of effector function.

While, with the exception of neutrophils, in healthy tissue cells the presence of A-type lamins is mostly associated with cell quiescence and differentiation, de-differentiation may again induce reduction of lamin A/C.53 Therefore, the downregulation of lamin A/C in many cancers, i.e. leukemia’s, lymphoma and small cell lung cancer, as well as some epithelial cancers, including breast, colon, gastric and skin carcinoma was originally explained with de-differentiation mechanisms.84 Reduced lamin expression has also been reported to correlate with tumor aggressiveness, where low expression levels of A-type lamins correlated with an increased recurrence of stage II and stage III colon cancer patients.85,86 However, in other cancers aggressiveness correlates with increased lamin A/C levels, i.e., in a subset of epithelial cancers, including ovarian, skin, colorectal and prostate cancer.84,96 Cancer-related changes in lamin expression mostly account to A-type lamins, with a small exception for B-type lamins, where subtypes of lung cancer and neoplasms in the gastrointestinal tract show a decrease in lamin B1 expression. All together, both lamin up- and downregulations are associated with cancers and thus de-differentiation is insufficient to explain lamin function with cancer.71,78,84

The correlation of lamin A expression with nuclear stiffness was demonstrated by a number of technical approaches. Overexpression of lamin A content in isolated Xenopus oocyte nuclei was directly associated with nuclear stiffness as demonstrated by atomic force microscopy (AFM).65,87 Accordingly, deficiency of lamin A/ C in mouse embryonic fibroblasts reduced nuclear rigidity and integrity as observed by a cellular compression device and nuclear strain experiments.67,88 In addition, lamin A/C knockdown in human primary fibroblasts yielded increased nuclear deformation by micropipette aspiration, with deformation levels similar to to embryonic stem cells, while B-type lamin levels remained unchanged.37,67 All these data support the concept that a high lamin A:B stoichiometry enhances rigidity of the nucleus.89 Interestingly, recent literature also suggests that B1-type lamins contribute to nuclear stiffness in fibroblasts, accounting to the disease effects in autosomal dominant leukodystrophy.90 In conclusion, lamin A expression levels significantly contribute to the overall stiffness of the nucleus and consequently the entire cell. Lamin A/ C expression is regulated by a number of mechanisms, with the ECM stiffness as an important contributor.

Impact of ECM stiffness on nuclear rigidity

The overall cellular and nuclear stiffness directly depends on the rigidity of the underlying or surrounding ECM.91-93 The cell
senses ECM stiffness by strengthened integrin binding to the ECM, mechanosensitive focal adhesion proteins that transmit signals to the cytoskeleton and subsequent reinforcement of actin filament strength and stiffening. Actin cables transmit these signals via the LINC complex and the nuclear lamina into the nucleus to switch on mechanosensitive gene expression. One potential transmission mechanism to switch on gene expression occurs through positional changes of chromatin territories during mechanical stress. One example of mechanosensitive gene expression is the linear positive correlation of lamin A expression with increasing tissues stiffness mediated by the retinoic acid pathway. Whereas lamin expression regulation is a relatively slow process over hours, lamina assemblies can be changed fast in response to changing stiffness of their surrounding by an expression-independent mechanism. This is based on a lamin assembly/disassembly balance mediated by fast lamin de-phosphorylation and phosphorylation processes. Increased cell spreading on stiff tissues suppresses lamin A phosphorylation, consequently stabilizing lamin A assemblies, whereas soft tissue contact supports partial lamin phosphorylation-dependent disassembly. Together, ECM stiffness-mediated signaling can affect nuclear deformability through transcriptional alterations by chromatin dislocations, activation/expression of stiffness-related genes including lamin A, or differential regulation of lamin turnover. Overall, nuclear stiffness is directly determined by chromatin organization, the nucleoskeleton (although not further reviewed here) and the level of assembled lamin, and regulated by the rigidity of the ECM environment. Dependent on these factors, nuclear rigidity can vary considerably and affect the capacity of a cell to migrate.

Consequences of Nuclear Deformability for Cancer Cell Migration

Space negotiation during migration is a reciprocal interplay between physical space and cellular and nuclear adaptation, respectively, which can both vary considerably. A decrease in matrix spacing leads to a decay in migration rates (Table 1) and, likewise, varying nuclear deformability depending on chromatin organization and nuclear lamina expression might modulate migration efficacy or arrest.

In regard to chromatin organization, cancer often associates with increased transcription rate and, in consequence, with concomitant nuclear shape alterations, together with increased nuclear pliability. This increased nuclear deformability might initially hint toward a function for increased migration rates under confined conditions. Instead, however, chromatin condensation and thus stiffening together with size reduction is favorable for cell migration. A rapid increase in histone methylation at H4K20me1, H3K27me3 locations leading to heterochromatin formation is required for the induction of directed migration in a wound healing assay. This hints toward an important structural role of chromatin to reduce nuclear size and to shape the nucleus for efficient cell migration in restricted space. Furthermore, chromatin is thought to be part of the nucleoskeleton, required for mechanical coupling of the nucleus to the cytoskeleton to facilitate efficient cell migration. Thus, chromatin/nucleoskeleton organization promotes migration most when keeping the nucleus in a compact form of smaller size.

Next, as summarized above, the progression of different cancers is often accompanied by an up- or downregulation of lamins, however, the impact of lamin expression on cancer invasion and migration only begins to be clarified. Currently, a growing body of evidence, based on in vitro data, hints toward an important role for lamin A/C in the migration of different cell types. Most data have been collected using 2-dimensional wound healing assays together with transmigration or synthetic channel assays of defined porosity. A number of studies show that enhanced lamin expression directly correlates with increased migration efficacy, e.g. in ovarian and colorectal cancers. Others show, with growing evidence, an inverse correlation of lamin A/C expression with migration efficacy in line with the principle that enhanced nuclear pliability is associated with increased invasion. Some of the contrasting outcomes may originate from the different physical dimensionalities of the migration substrates and the fact that lamin modulation-induced disturbed mechanocoupling cannot be compensated on a 2D substrate surface. Thus downregulation of lamin A/C which is associated with increased nuclear deformability may promote tumor cell dissemination, particularly in dense tissues, which might be, however, on the cost of cell survival. In conclusion, chromatin organization regulates the density and size, and lamin A/C expression the pliability of the nucleus, and together impact cell migration in vitro.

Conclusion

The concept of space negotiation, summarized in this review, is valid for metastatic cancer invasion through the dense ECM of reactive tumor stroma, but applies in general to all cell types migrating through dense tissue spaces, such as fibroblasts or immune cells. Whereas tumor-related ECM remodeling processes were studied extensively during the last decades, the mechanisms of cell, and in particular nuclear deformation, to adapt to small available tissue spaces during migration has only recently begun to be investigated and still leaves open questions. The expression levels of lamins, most importantly lamin A/C, correlate with nuclear stiffness, however, do not unambiguously correlate with the capacity to invade. In addition, for the progression of various human cancers both lamin up- and downregulation have been reported. It is therefore not yet possible to clearly assign lamin expression rates to cancer invasion rates, survival and metastasis formation in the living organism. Systematic screenings of different tumor locations, such as main mass, non-invasive, invasive or metastatic zones may help to elucidate the role of lamins in disease progression. Another, related, future goal might be to deeper address the role of nucleoskeleton-enveloping as well as intranuclear actin structures that help to transport and deform the nucleus for migration against confining resistance within 3-dimensional structures. As a recent achievement it was shown that nuclear actin organization by nuclear Račl contributes to the ability of the nucleus to deform and drive invasion. It remains a future challenge to test the relevance of actin- and lamin-mediated cell mechanics in the context of invasive space negotiation to better understand -and target- metastatic invasion in vivo.
Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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