



Organelle adaptations in response to mechanical forces during tumour dissemination

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Abstract

Cell migration plays a pivotal role in various biological processes including cancer dissemination and successful metastasis, where the role of mechanical signals is increasingly acknowledged. This review focuses on the intricate mechanisms through which cancer cells modulate their migratory strategies via organelle adaptations in response to the extracellular matrix (ECM). Specifically, the nucleus and mitochondria emerge as pivotal mediators in this process. These organelles serve as sensors, translating mechanical stimuli into rapid metabolic alterations that sustain cell migration. Importantly, prolonged exposure to such stimuli can induce transcriptional or epigenetic changes, ultimately enhancing metastatic traits. Deciphering the intricate interplay between ECM properties and organelle adaptations not only advances our understanding of cytoskeletal dynamics but also holds promise for the development of innovative anti-metastatic therapeutic strategies.

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Introduction

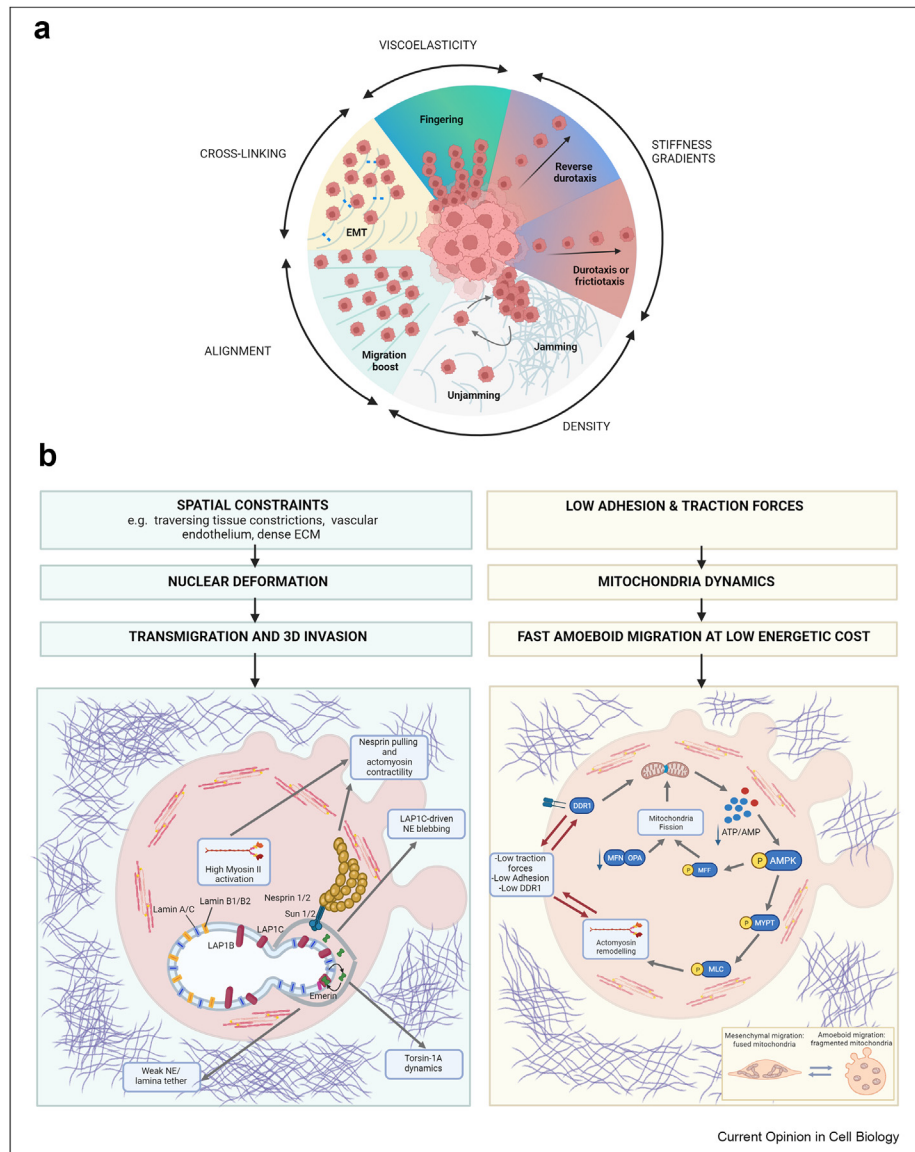
Cell migration is essential for immune responses, development, and cancer, where different individual and collective migration strategies have been described [1–4]. These migration modes are influenced by the

extracellular matrix (ECM) and cell-cell interactions. Individual strategies of mesenchymal and amoeboid migration rely to different extents on Myosin II activity, adhesion, matrix degradation, and actin dynamics [5]. Collective cell migration is characterised by the synchronised movement of multiple cells, maintaining physical connections through cell–cell contacts while coordinating their actin dynamics and intracellular signalling [6].

Cells sense and react to physical cues in their environment by converting mechanical signals into biochemical responses, a phenomenon known as mechano-transduction [7]. Beyond this responsiveness, cells actively alter their mechanical surroundings through mechano-reciprocity, a crucial process influencing the plasticity of cell migration, tissue architecture, and cell fate [8]. In the context of cancer, the interaction between cells and ECM is of particular importance. As malignant cells proliferate and spread, they encounter diverse mechanical stresses within the tumour microenvironment (TME) [9]. Both cancer cells and other TME cellular constituents, such as fibroblasts and immune cells, remodel their surrounding matrix [10]. The reconfiguration of the tumour-associated matrix is a prominent feature of solid tumours [10]. Metastatic cancer cells adapt to varied environments, responding to changes in ECM properties including alterations in stiffness, topography, crosslinking, viscoelasticity, and porosity (Figure 1(a), Table 1), which allow their escape from the primary tumour and colonisation of new organs. Notably, specific ECM characteristics influence the migration trajectory and velocity of cancer cells, ultimately facilitating dissemination (Box 1). For instance, matrix stiffness and viscoelasticity play pivotal roles in regulating cancer dissemination (Box 1) [11], driving spheroid symmetry breaking and epithelial-to-mesenchymal transition (EMT) [12]. Understanding the mechanisms through which specific ECM conditions promote tumour progression holds promise for the development of novel cancer therapies targeting the dissemination steps.

Cytoskeletal remodelling stands at the forefront of mechano-transduction, exerting a profound influence on plasticity of cancer cell migration. It orchestrates crucial

Figure 1



ECM properties and nuclear-mitochondrial adaptations favouring tumour dissemination. (1a) Clockwise, representation of viscoelasticity, stiffness, matrix density, alignment, and crosslinking. Viscoelasticity, depicted with a colour gradient representing stress changes over time, influences finger-like extensions and tumour progression. Gradual shift from red to blue indicates decreased stiffness, prompting negative durotaxis, while increased stiffness supports durotaxis. Increased stiffness/friction in absence of adhesion can also induce frictotaxis. Dense matrices lead to jamming and liquid-like migration, whereas loose matrices result in unjamming and gas-like dissemination. Alignment facilitates migration. Matrix fibre crosslinking, represented by dotted lines, promotes Epithelial–Mesenchymal Transition (EMT) and tumour progression. The double arrows outside the circles indicate that these matrix properties are not interdependent but mutually affect one another. **(1b)** The left panel illustrates the enrichment of LAP1 expression in amoeboid migrating cells, with nuclear envelope (NE) blebs. LAP1C, in a Lamin-A/C-dependent manner, specifically localizes to NE blebs, facilitating the passage through physical constraints by virtue of its relatively weaker N-terminal NE/lamina tethering, thereby promoting NE blebbing. Right panel B, weakly adhesive rounded-amoeboid cancer cells with high cortical Myosin II activity and low levels of Discoidin Domain Receptor 1 (DDR1) collagen receptor. These cells apply low-magnitude traction stress to the extracellular matrix (ECM) due to their reduced adhesion requirements. Low matrix adhesion associated with lower ATP levels results in an AMP imbalance and subsequent activation of AMP-activated protein kinase (AMPK). Active AMPK, in turn, phosphorylates the regulator of cytoskeletal dynamics, Myosin phosphatase target subunit 1 (MYPT1), leading to an overall increase in Myosin II activity. Simultaneously, active AMPK induces mitochondrial fission through the phosphorylation of Mitochondrial Fission Factor (MFF). Inset illustrates how mesenchymal and amoeboid modes of migration are characterised by different mitochondrial morphologies.

aspects of cellular behaviour, including morphology, motility, and tension, serving as a central conduit for transmitting forces during migration. This process

integrates both mechanical and biochemical signals, engaging with signal transduction pathways that drive migration, invasion, survival, and ultimately metastasis.

Table 1

Glossary of key features relating to physical ECM parameters and responses of cell migratory behaviour.

Term	Definition	Reference
Mechanotransduction	The process by which cells convert mechanical stimuli from their environment into biochemical signals.	[7]
Mechano-reciprocity	The dynamic and bidirectional interaction between cells and their mechanical environment.	[8]
Stiffness	A measure of Young's modulus and substrate elasticity, referring to the resistance to deformation under applied force.	[11]
Durotaxis	Mechanism of directional migration where cells respond and migrate up an extracellular stiffness gradient.	[22,23]
Negative durotaxis	Mechanism of directional migration where cells respond and migrate towards softer substrate stiffness.	[24]
Collective durotaxis	Cell groups migrating cohesively in response to stiffness gradients, reflecting coordinated mechano-transduction and enhanced efficiency of durotaxis.	[23,25,26]
Molecular clutch model	Mechanism where integrin binding and actin polymerisation at the front of the cell generates traction force and promotes stiffness-driven directional migration.	[27]
Frictotaxis	Adhesion-independent durotaxis, where cells respond to frictional forces during migration.	[28–30]
Viscoelasticity	The capacity of a material to exhibit both time- and rate-dependent elastic (shape-recovering) and viscous (flow-resisting) behaviours under stress-induced deformation.	[31]
Stress relaxation	The gradual decrease in stress experienced by the tissue over time when it is subjected to a constant strain or deformation.	[32]
Topography	Spatial and geometric architecture of extracellular matrix (ECM) components, including fibre alignment.	[33]
Porosity	The extent of open spaces in the tumour microenvironment (TME), allowing both diffusion of nutrients and oxygen, but also controlling constrained migration.	[34]
Crosslinking	ECM crosslinking, catalysed by enzymatic reactions controlling the chemical bonds between structural proteins and ECM components determining structural integrity.	[10]
Cell jamming and unjamming	Collective invasion of cells induced by tissue confinement, determined by cell density, cell–cell adhesion, mechanical forces and tension, and results in the individualisation of cells in a gas-like mode.	[35,36]
Intratumoural pressure	Elevated intra-tumoural pressure impacts cell migration within tumours, created by tumour mass growth, vascular compression, vascular leakiness, increased interstitial fluid, ECM stiffness, inflammatory infiltration and tissue remodelling.	[37]
Shear stress	The force exerted by vascular flow on vessel lining (endothelium) and circulating cells (CTCs, immune cells), determined by fluid flow rate, viscosity and physical dimensions.	[38]

While the significance of matrix-driven cytoskeletal rearrangements during cancer progression has been extensively discussed elsewhere [13,14], this review directs its focus towards subcellular structures, particularly the nucleus and mitochondria.

Organelle adaptation during mechano-transduction is crucial for cancer migration plasticity due to its multifaceted impact on cellular processes [15,16]. How cytoskeleton and organelles influence each other is crucial for integrating at the whole cell level the specific energy demands associated with cancer cell migration [17], amidst fluctuating mechanical

conditions [18,19]. Notably, cancer cells persistently exposed to challenging environments develop transcriptional responses linked to organelle mechano-sensing [20].

Emerging evidence points at organelle adaptations as key responses to mechanical forces and as essential strategies employed by cancer cells to enhance migration and tumour progression [17,20,21]. This review explores how matrix-dependent nuclear and mitochondrial adaptations translate into intracellular responses, such as rapid metabolic changes and long-term transcriptional alterations.

Box 1. ECM properties regulating cancer migration.

The ECM plays a pivotal role in regulating cancer migration. A key factor governing this interplay is matrix stiffness, which can range from soft in the brain (≤ 1 kPa) to rigid in the bone (15 GPa) [8]. This variance in stiffness not only impacts tumour dissemination and survival [10], but also immune activation [39], underscoring its critical role in cancer biology.

Cells sense and respond to stiffness through changes in their cytoskeleton and focal adhesions, where stiffer substrates promote actin polarisation [40]. This process is intricately linked to durotaxis, where cells migrate towards stiffer substrates, facilitated by integrin binding and actin polymerisation at the cell front [22,23,27]. Originally observed in single cells during development and cancer, durotaxis describes cells' intrinsic preference for substrates that provide 'optimal stiffness' for maximising traction forces [41]. Interestingly, negative durotaxis has been described in glioma cells, which can migrate towards softer substrates [24], highlighting the complex methods employed by migrating cells.

Durotaxis extends beyond individual cell movement to collective movement, vital in processes such as epithelial and neural crest migration. Within cell clusters, durotactic capacity of single cells is enhanced through local stiffness-sensing at the periphery, coupled with cell–cell junctions crucial for long-range force transmission [25,26,42]. Importantly, cells are also able to migrate in stiffness-independent modes [43]. Emerging work has challenged the view that all cells require specific surface attachments to sense stiffness, as some cells instead use friction to move in response to differences in surface friction [28,29]. This sheds light on how adhesion-independent migration, such as some amoeboid migratory modes, could respond to differences in friction, but this remains to be explored *in vivo*. Furthermore, non-adherent collective amoeboid migration has been observed, via coordinated actomyosin contractility at the rear and fluctuating cell jiggling to direct migration [30]. Cells could therefore respond to gradients in both stiffness or friction at the tumour edge, or within tissues far removed from 'optimal' stiffness ranges requiring specialised migration strategies.

ECM crosslinking is another factor regulating cancer progression, promoting matrix stiffness, cancer motility and immune cell infiltration and activation [10,44]. Lysyl oxidase (LOX) plays a key role in this process, mediating crosslinking and promoting a fibrotic environment conducive of cancer growth and dissemination [45]. Interestingly, inhibition of fibre crosslinking improves T cell infiltration and efficacy of immunotherapies, highlighting how matrix perturbation offers a promising therapeutic strategy [46].

ECM complexity is further characterised by its different topographies, varying between 2D and 3D, the latter inducing bleb-based migration [47]. The diversity in physical landscape requires cells to translate biomechanical signals via mechano-transduction [33]. Leukocytes use topographical cues for propulsion, where actin retrograde flow aligns with substrate texture [48]. The alignment of matrix fibres can create directional cues, promoting migration and invasion by generating anisotropic stress [49–51]. Fibre orientation combined with proteolytic remodelling serves as a powerful driver of persistent and rapid migration of cells away from the primary tumour [52–54]. Challenges such as small matrix pore sizes can limit cell migration by restricting nuclear deformation [34]. To circumvent this, metastatic cancer cells increase nuclear envelope (NE) blebbing, in addition to regulating actomyosin contractility [21,55]. Moreover, denser matrices can promote collective migration [35,36], while actomyosin contractility is critical during confined individual cell migration [47] and collective amoeboid migration [30]. Therefore, both topography and force sensing are crucial for migration and invasion, where fibre orientation and alignment is spatially-dependent [56].

Finally, intra-tumoral compressive stresses support invasive and proliferative behaviours [37] indirectly via promoting migration through fibroblast activation and desmoplasia [57,58]. Mechanical confinement results in jamming and unjamming transitions which are important in cancer dissemination [36]. Taken together, the ECM and extracellular forces within the tumour orchestrate physical cues and cellular responses, acting as essential regulators of cancer cell migration plasticity.

Physical control of organelle dynamics during cancer cell migration

It is increasingly evident that organelles play pivotal roles in sensing physical cues to coordinate cell movement. The nucleus, due to its robust connections to the cytoskeleton, stands out as a key regulator of migration [59–62]. Facilitating this coupling between the cytoskeleton and nucleus are LINC complexes, which transmit mechanical signals from the cell membrane to the chromosomes [63]. Actin polymerization, on the other hand, directly impacts the nucleus, aiding its passage through constrictions in 3D environments [64]. Mechanical forces transmitted from cellular adhesions to the nucleus can induce rapid chromatin stretching within seconds, a phenomenon linked to the activation of mechanosensitive gene expression. However, the precise mechanisms conferring specificity to this force-induced activation of particular genes remains an unresolved question, especially in cancer research [15]. The

cytoskeleton and LINC complex jointly regulate the translocation of transcription factors to the nucleus. For instance, matrix rigidity, focal adhesions, and the LINC complex regulate YAP translocation to the nucleus [65,66].

The nucleus, being the stiffest and largest organelle, presents a significant challenge during 3D migration. The nuclear envelope (NE) serves as a sensor of cellular deformation, initiating mechano-transduction pathways that regulate actomyosin contractility and cell migration [61,62]. This enables cells to adjust their behaviour in response to the specific conditions of their surrounding tissue microenvironment to sustain migration.

As cells navigate through confined spaces, they must protect their genome while contending with forces that can lead to NE ruptures and DNA damage. Notably, cancer cells exhibit increased resilience to nuclear

deformation during migration and employ mechanisms like the endosomal sorting complex required for transport III (ESCRT III) machinery to repair NE ruptures [60]. Moreover, coordinated actions between the nucleus and cytoskeleton are crucial during 3D migration, with Lamin A/C, actin stress fibres, Myosin II, and the LINC complex playing pivotal roles in navigating constrictions and regulating NE tension. Dynamic variations in the levels of Lamin A/C and vimentin expression under confinement create a feedback loop, enhancing amoeboid migration by regulating nuclear deformability while preserving cell viability [67]. Metastatic cancer cells with high ROCK-Myosin II activity use NE blebs to increase nuclear flexibility [21], while NE rupture-repair events have also been observed. Mechanistically, lamin-associated polypeptide 1 (LAP1), particularly its shorter isoform LAP1C, along with controlled Torsin dynamics, supports nuclear envelop bleb generation, releasing nuclear tension and facilitating tumour transmigration and 3D migration both *in vitro* and *in vivo* [21] (Figure 1(b), left panel). Interestingly, while DNA damage induced by nuclear ruptures triggers senescence in non-transformed cells, it promotes invasive behaviour in breast cancer cells [68]. Moreover, repeated mechanical constriction increases resistance to anoikis, fostering breast cancer motility and invasiveness [69], maybe due to changes in gene expression as a result of epigenetic modifications induced by chromosome structural changes [70,71]. This body of work suggests that nuclear adaptations due to physical limitations confer active nuclear mechano-sensing properties during cell migration.

Less is known about mechano-transduction in other organelles [16,72]. Nevertheless, mitochondria are arising as key players during cell migration. Several links between the actin cytoskeleton and mitochondria have been established. Actin-binding proteins (ABPs) and

the actin cytoskeleton interact with mitochondria to control their dynamics, biogenesis, and mitophagy. Additionally, mitochondrial factors like ATP, ROS, Ca²⁺ and metabolites play a direct role in influencing ABP-mediated actin dynamics and cell migration (extensively reviewed in [73]).

Moreover, recent findings highlight the influence of ECM properties on mitochondrial dynamics. Some studies associate matrix stiffness with mitochondrial fission, while others report stiffness-induced mitochondrial fusion [18,19,74,75]. These differences may arise from variations in experimental settings, including different 2D/3D substrates (fibronectin, collagen, polyacrylamide), disparities between normal and cancer cells, and metabolic differences among tumour types and their oncogenic backgrounds. Moreover, mitochondrial dynamics could differ from tumour initiation to dissemination. For instance, breast cancer cells respond to changes (increased [18] or decreased [75]) stiffness by increasing mitochondrial fission (Table 2) suggesting that mitochondria are stress sensors.

During migration, mitochondria undergo shape, size, and positional adjustments within the cell to meet energy demands, providing fuel necessary for cytoskeletal rearrangements, membrane dynamics, and adhesion turnover. Mitochondrial trafficking to the leading edge, in response to local AMPK activation, facilitates localised ATP production at sites of actin remodelling [76]. Moreover, AMPK, serving as a mechano-metabolic sensor, integrates signals downstream of ECM receptors [17]. Lower matrix adhesion requirements in amoeboid migrating cancer cells correlate with reduced ATP mitochondrial levels, leading to an AMP imbalance that activates AMPK. This activation results in the phosphorylation and inactivation of Myosin phosphatase

Table 2

Summary of mitochondrial responses upon changes in ECM properties.

Matrix manipulation	Experimental setting	Mitochondrial responses	Cell type	Reference
Increasing stiffness	Fibronectin-coated polyacrylamide hydrogel (from 400 Pa to 60 kPa)	Drives mitochondrial stress response that induces mitochondrial fission	Human mammary epithelial cells and breast cancer cells	[18]
	Polyacrylamide hydrogels (from 1 kPa to 20 kPa)	Drives mitochondrial fission via DRP1 and MFF for durotactic migration	Primary lung fibroblasts	[74]
Decreasing stiffness	Fibronectin-coated hydrogels (from 700 Pa to 38 kPa)	Drives mitochondrial fusion	Pancreatic cancer cells	[19]
	From fibronectin-coated hydrogels (700 Pa) to glass (2–4 GPa)			
	Fibronectin-coated polyacrylamide hydrogels (from 15 kPa to 500 Pa)	Drives DRP1 and MIEF1/2 mediated mitochondrial fission	Mouse model of metastatic breast cancer cells dormant in the lung soft tissue	[75]
	Collagen I-coated polyacrylamide hydrogels (from 50 kPa to 200 Pa)			
	Matrigel (from 1 GPa to 250 Pa)			

(MYPT1), enhancing Myosin Light Chain II phosphorylation necessary for efficient amoeboid migration. Simultaneously, AMPK promotes Mitochondrial Fission Factor (MFF) phosphorylation, favouring mitochondrial fission and reducing mitochondrial activity, thus sustaining AMPK activation and amoeboid migration [17] (Figure 1(b), right panel).

Although mitochondrial dynamics and the actin cytoskeleton are inter-connected, we are still far from a full understanding of how cells integrate mechanical signals from the microenvironment, translate them into mitochondrial structural and functional changes that will lead to short- or long-term changes in migratory behaviours.

Changes and adjustments in mitochondrial function significantly rely on the nucleus (more than 95% of the proteins found in mitochondria are encoded by nuclear DNA) [77]. However, no stable physical structures have been described between mitochondrial and nuclear membranes. Nonetheless, considering the interactions of both mitochondria and nuclei with the endoplasmic reticulum (ER) [16,78], there is a plausible scenario where the dynamics of mitochondria and nuclei might be intertwined. Moreover, the cytoskeleton could act as a physical connector between these separate intracellular compartments. Future studies are needed to fully understand how cells integrate physical cues to modulate cellular decisions by globally controlling organelle dynamics crosstalk.

Organelle mechano-sensing: metabolic changes driving tumour migration plasticity during metastatic dissemination

Mitochondria and nuclei sense mechanical signals and translate them into fast metabolic changes, which facilitate cell migration plasticity. Nevertheless, sustained mechanical stress could potentially lead to long term transcriptional or epigenetic changes supporting metastatic behaviour [15,79].

The physical properties of the ECM emerge as crucial regulators of cellular energy demands [36]. Rigid and densely structured matrices are an obstacle for migrating cells and increase energy requisites due to the demands on cytoskeletal remodelling [19,80–82]. In the context of fibrotic cancers, cells sustain elevated ATP production to preserve sufficient energy levels in challenging microenvironments [19,81]. Pancreatic cancer cells can maximise energy flow via ATP recycling through CKB-mediated phosphocreatine production during invasion [19]. Denser matrices can induce a shift towards fluid-like collective migration of breast cancer cells irrespective of E-cadherin status [20,36]. During this process, cancer cells coordinate their movements like a cyclist *peloton*. Leader cells increase glucose uptake or expression of OXPHOS genes to support increased

energy demands, whereas follower cells exhibit a relative insensitivity to matrix stiffness changes [82]. This strategy allows cells to offset the energy demand by switching between leader and follower roles, effectively reducing the lifetime of leader cells [82]. In loose, soft matrices, breast cancer cells undergo a process of individualization, allowing for energetically favourable, gas-like dissemination [36,82]. This mode of migration may provide a partial explanation for why certain cancer cells can move towards softer tissues. The orientation of matrix fibres emerges as a crucial factor dictating the extent of local tumour invasion into surrounding tissues [83]. In breast cancer cells, Rho–ROCK signalling promotes the alignment of collagen fibres perpendicular to the tumour boundary, facilitating a more energy-efficient 3D migration and invasion [80]. Significantly, this alignment of collagen fibres is correlated with a poorer prognosis in breast cancer patients, highlighting its relevance in clinical outcomes [84].

Migrating cancer cells select the path of least resistance [85] by using evolved mechanisms that reduce their ATP requirements [17]. Mitochondrial dynamics and functions are integral factors in orchestrating energy regulation, especially in the context of cancer cell migration [80]. In amoeboid migratory and metastatic melanoma cells with lower matrix adhesion levels, lower OXPHOS, lower mitochondrial activity and higher AMPK are required for 3D invasion. Importantly, this mitochondrial adaptation becomes a vulnerability as AMPK inhibition reduces amoeboid cancer cell metastatic colonisation abilities [17]. Furthermore, in breast and head and neck (HN) carcinoma cells, hypoxic conditions induce downregulation of adhesion and energy metabolism through calpain-2-mediated cleavage of talin-1. This leads to individualization and activates an eco-mode of cancer dissemination characterised by bleb-based amoeboid migration. Inhibiting calpain-2 halts the amoeboid transition, thereby diminishing hypoxia-inducible factor (HIF)-dependent metastasis. Targeting calpain-2 therefore emerges as a strategic approach to block HIF-driven metastatic dissemination [86]. Accordingly, lower expression of OXPHOS genes positively correlates with metastatic potential across different cancer types [87].

On the other hand, nucleo-cytoskeletal mechano-sensing leads to short term metabolic plasticity. When the nucleus of a migrating cell encounters constraints, the unfolding of the NE triggers the activation of calcium-dependent phospholipase cPLA2 and the release of arachidonic acid (AA), ultimately culminating in the stimulation of ATP-dependent Myosin II activity and facilitating rapid amoeboid migration [61,88].

As mentioned above, emerging evidence points to external forces as key regulators of nuclear functions including transcriptional reprogramming. Downstream

of physical cues, key events are chromatin remodelling changes and engagement of mechanosensitive transcription factors [15]. Notably, in response to such mechanical cues, YAP translocates to the nucleus via stretched nuclear pores, altering gene expression [66]. Persistent nuclei deformation can promote specific transcriptional programs to support tumour progression and dissemination. Invasive breast cancer cells undergo unjamming and individualization processes experiencing loss of nuclear integrity, leading to cGAS–STING cytosolic DNA responses. This specific event promotes invasive traits and the emergence of drug-resistant features in breast cancer [20].

Within environments lacking an ECM, such as biological fluids, shear forces impact migratory plasticity. In response to these conditions, some cells exhibit a clustering behaviour, serving as an effective strategy to mitigate the adverse effects of reactive oxygen species (ROS), while elevated pyruvate levels play a role in supporting the survival and adaptation of circulating tumour cells [89]. Whether shear forces initiate transcriptional rewiring is yet to be established.

In addition to mitochondrial and nuclear mechanosensing, other organelles translate mechanical cues into metabolic and transcriptional changes. In mammary epithelial cells, the Golgi apparatus shows mechanosensitivity in softer matrices connecting actomyosin levels with Lipin-1, leading to SREBP transcription factor activation, stimulating lipid synthesis [90]. How breast cancer cells organise their Golgi in similar conditions or whether these mechanisms play a role during cell migration remains to be tested. Moreover, pannexin-1 is a non-selective endoplasmic reticulum (ER) channel endowed with mechanosensitive properties, and has been reported to mediate ATP release [16]. However, how the Golgi apparatus and/or ER modulate cell migration in response to mechanical cues during tumour progression remains poorly understood.

In summary, the plasticity of cell migration allows cells to selectively adopt the most energy-efficient migration strategy through the coordination of mitochondrial and nuclear mechanosensing, as illustrated in [Figure 1\(b\)](#). Prolonged exposure to external physical forces originating from the TME induces nuclear transcriptional changes, potentially supporting other biological processes important for metastasis.

Conclusion and future perspectives

In this review, we discuss how mechanical cues from the ECM are integrated by cellular organelles to support cancer cell migration and invasion. We focus on the nucleus and the mitochondria, since they play key functions supporting cell migration in different time scales.

Highly metastatic cells adapt their mitochondria to disseminate at a low energetic cost. Similarly, the nuclei of metastatic cells are more plastic via producing NE blebs that release tension from the nuclei and facilitate migration through confined spaces during local invasion and distant dissemination. While it is evident that aberrant matrix remodelling enhances cancer migration, our understanding of how specific ECM properties trigger advantageous organelle adaptations in cancer is still limited. Understanding how matrix organisation and composition alters organelle dynamics and functions favouring tumour dissemination will allow the development of novel anti-metastatic treatments.

Understanding if organelle plasticity is a hallmark but also a vulnerability of metastatic cancer cells will require a multidisciplinary approach in which cell biology is combined with the latest cancer models. Advanced imaging techniques (digital pathology) spatial multi-OMIC-based technologies (transcriptomics, epigenomics and metabolomics) in patient tissue samples will allow identification of adequate biomarkers for organelle plasticity. Patient-derived xenografts (PDX) and organoids (PDO) more closely recapitulate human disease and will allow mechanistic and functional studies to complement traditional cell line approaches. Second-harmonic generation microscopy, coupled with electron microscopy, will allow the study of both matrix organization and organelle features. All these combined approaches will contribute to the identification of transcriptional and metabolic vulnerabilities.

Artificial intelligence (AI) could be used to translate this information into clinical applications. Generative AI holds the potential to forecast organelle and molecular profiles through the analysis of tumour biopsies. Notably, the integration of histopathological assessments of invasive cells, including the evaluation of nuclear and mitochondrial characteristics, will allow pathologists to establish important correlations between cell/tissue biomarkers and metabolic, transcriptional, or epigenetic vulnerabilities.

This advancement will prove invaluable for differential diagnosis and for cancer patient stratification, ultimately facilitating identification of compounds that selectively target the pool of metastatic cancer cells displaying advantageous organelle adaptations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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