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Unjamming Transition as a Paradigm for Biomechanical Control of Cancer Metastasis

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ABSTRACT

Tumor metastasis is a complex phenomenon that poses significant challenges to current cancer therapeutics. While the biochemical signaling involved in promoting motile phenotypes is well understood, the role of biomechanical interactions has recently begun to be incorporated into models of tumor cell migration. Specifically, we propose the unjamming transition, adapted from physical paradigms describing the behavior of granular materials, to better discern the transition toward an invasive phenotype. In this review, we introduce the jamming transition broadly and narrow our discussion to the different modes of 3D tumor cell migration that arise. Then we discuss the mechanical interactions between tumor cells and their neighbors, along with the interactions between tumor cells and the surrounding extracellular matrix. We center our discussion on the interactions that induce a motile state or unjamming transition in these contexts. By considering the interplay between biochemical and biomechanical signaling in tumor cell migration, we can advance our understanding of biomechanical control in cancer metastasis.

1 | Introduction

Cancer remains the second most common cause of death in the United States, behind heart disease (Xu et al. 2021). This is due, in part, to the challenges associated with treating metastatic cancers, which account for 90% of all cancer-related deaths (Steeg 2016; Kumari et al. 2023; Welch and Hurst 2019). Metastasis is the process of invasive cancer cells leaving the primary tumor site, circulating through the bloodstream, and then colonizing and forming secondary tumors in different organ systems (Steeg 2016; Welch and Hurst 2019; Gensbittel et al. 2021; Fares et al. 2020; Massagué and Obenauf 2016). Recent advances in metastatic cancer treatment involve drug and antibody therapies that target metastatic behaviors (Steeg 2016; Kumari et al. 2023; Welch and Hurst 2019). However, outcomes in Food and Drug Administration (FDA) trials have been mixed with respect to their effectiveness for different cancer types and stages. Thus, there is a pressing need for a better understanding of the progression to metastasis from the original tumor, which begins with biochemical and physical cues that initiate tumor cell migration.

Tumors are complex, multicellular systems that can be considered ecosystems, wherein tumor cells engage in heterotypic interactions with neighboring cells and their broader microenvironment (Tabassum and Polyak 2015; Schulz et al. 2019;

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Baghban et al. 2020). These complex interactions between cells and the surrounding environment dictate overall cell proliferation, tumor longevity, and migratory phenotypes (Tabassum and Polyak 2015; Schulz et al. 2019; Baghban et al. 2020; Egeblad, Nakasone, and Werb 2010; Yamada and Sixt 2019; Cox 2021). Tumor cell migration can be triggered by biochemical signals from the microenvironment, including the secretion of growth factors and cytokines that enable cancer cells to detach from the primary tumor (Merino-Casallo et al. 2022; Plou et al. 2018). Such biochemical stimuli influence the mode of migration, determining whether tumor cells undergo individual or collective migration (Merino-Casallo et al. 2022).

There is abundant evidence supporting collective tumor cell migration, which relies on both cell–cell and cell-extracellular matrix (ECM) interactions (Yamada and Sixt 2019; Cox 2021; Lintz, Muñoz, and Reinhart-King 2017; Ladoux and Mège 2017; Chaudhuri et al. 2020). In collective migration, cells must coordinate their movement with neighboring cells, which is facilitated by mechanosensitive adhesive complexes between cells and the substrate (Yamada and Sixt 2019; Merino-Casallo et al. 2022; Ladoux and Mège 2017; Mayor and Etienne-Manneville 2016). Furthermore, tumor cells interact with and migrate through the ECM, where the physical characteristics of the ECM shape cell behavior (Cox 2021; Wirtz, Konstantopoulos, and Searson 2011; Liu, Chaudhuri, and Parekh 2017; Saraswathibhatla, Indana, and Chaudhuri 2023; Eble and Niland 2019). Consequently, there has been a push in the field to investigate the role of mechanical forces on tumor cell migration.

Tumor cells experience compressive forces resulting from cell proliferation within solid tumors, cell–cell adhesion complexes, and cell-ECM interactions. There is a growing body of work demonstrating the role of compressive forces in the regulation of cancer cell invasion (Liu, Chaudhuri, and Parekh 2017; Luo et al. 2022; Cai et al. 2022, 2024; Tse et al. 2012; Barbazan et al. 2023). Also, it has been recently proposed that invasive cancer cells retain a "mechanical memory" from mechanotransduction and epigenetic changes within the tumor microenvironment (TME) (Cambria et al. 2024; Nasrollahi et al. 2017). Thus, researchers are now exploring mechanobiological strategies in the development of new cancer treatments, which warrants further investigation into the biomechanical pathways that lead to tumor progression (Kumari et al. 2023).

In this review, we discuss how mechanical factors signal cells to transition from a static to a motile state (i.e., unjamming transition). The jamming transition describes the switch of collective granular materials from a solid-like to fluid-like state. Various mechanical properties propagate within and outside of these collectives that cause these transitions to arise. We first introduce the concept of jamming and how it can extend from describing behaviors of granular materials to biological systems, such as cancer cells within solid tumors. We next present a model whereby tumor cells are sorted based on adhesive properties, promoting cells with low adhesion and more motile behavior to the periphery of the tumor. Then, we discuss how (1) cell–cell interactions within the tumor and (2) ECM biomechanical properties promote unjamming transitions initiating cancer metastasis. Elucidating the physical contributions of the TME to cancer cell migration will provide insight into treating lethal metastatic cancers.

2 | Jamming Transitions in Cancer Cell Invasion Govern the Shift Between Static and Motile States

Jamming was initially introduced to explain the behavior of granular materials and describes a transition from a solid-like state to a fluid-like state (Liu and Nagel 1998; Zhang et al. 2010; Behringer 2015; Behringer and Chakraborty 2018; Trappe et al. 2001; Cai, Harada, and Nordstrom 2021; Chang 2022). In collective granular systems, jamming represents a transition from a flowing state to a rigid state (Zhang et al. 2010; Behringer 2015). These transitions have been observed in a wide variety of systems, ranging from molecular liquids to granular matter to soft materials (Behringer 2015; Das, Vinutha, and Sastry 2020; Pajic-Lijakovic and Milivojevic 2019). In the process of jamming, the viscosity of granular particles, such as coffee beans or sand grains, increases with density. As the particles become denser, they undergo a phase transition in which friction between particles slows them down, hinders neighbor exchanges, and causes the material to become more viscous or solid-like (Liu and Nagel 1998; Behringer and Chakraborty 2018; Ciamarra, Nicodemi, and Coniglio 2010; Meng et al. 2020). Squeezed grains become so tightly packed that they lose their ability to flow and maintain their shape (Brown et al. 2010). In soft matter and glassy materials, the density, temperature, and load (e.g., shear stress) are key parameters controlling the transition between an unjammed, deformable state and a jammed, solid-like state (Liu and Nagel 1998).

These principles of jamming extend beyond simple physical examples and have applications in understanding biological tissues (Garcia et al. 2015; Kang et al. 2021; Lawson-Keister and Manning 2021; Blauth et al. 2021). In fact, cells in dense tissues may be thought of as behaving like granular materials, becoming tightly packed and arrested in a jammed state, where cell movement is restricted. This raises the question of whether biological tissues exhibit similar jamming dynamics, with cells transitioning between fluid-like and solid-like states depending on their environment and external forces (i.e., load). Could cells in dense tissues be considered a collection of granular materials arrested in a jammed state?

In cellular systems, jamming is associated with the arrest of collective cell migration. Jamming is an inhibiting mechanism that describes a rigidity transition caused by the mutual hindrance of cells (Sadati et al. 2013; Atia et al. 2018; Bi et al. 2016; Lenne and Trivedi 2022). In the context of cancer, most invasive cells infiltrate collectively, and cancer aggression is more closely linked to collective cell migration than to single-cell migration (Blauth et al. 2021; Oswald et al. 2017; Haeger et al. 2014; Cheung et al. 2016; Yang et al. 2019; Yamamoto, Doak, and Cheung 2023). The process of jamming occurs when cellular rearrangements are diminished, and the cells become constrained by their neighbors (Bi et al. 2016). Consequently, jamming can arrest collective cell migration in both developmental and disease events. This phenomenon typically occurs at high cell densities and in cells with elevated adhesion expression, leading to a solid-like state.

In the following sections, we first discuss cell jamming under the condition of high cell density as found in a tumor, followed by the observations of soft and stiff cells that tend to congregate together. We will next discuss cell sorting due to cell rearrangement and suggest that this is a potential prerequisite for cell invasion into the ECM. Finally, we will describe the various modes of 3D migration once the tumor cells invade and compare the unjamming transition to the epithelial-mesenchymal transition (EMT).

2.1 | Cell Jamming Occurs at High Cell Density, Such as in Solid Tumors

Cell jamming and unjamming, considered key phenotypes in tissue development and cancer progression, describe transitions between solid-like (jammed) and fluid-like (unjammed) states, regulated by key factors such as cell density, cell–cell adhesion, and cell motility (Blauth et al. 2021; Atia et al. 2021). These shifts in cell state are also influenced by cell contractility, mechanical stress, and cell shape, as investigated in breast cancer (Cai et al. 2022; Park et al. 2015; Yang et al. 2017), bronchial (Cai et al. 2022; Park et al. 2015; Yang et al. 2017), and in silico (Cai et al. 2022; Park et al. 2015; Yang et al. 2017) migrating epithelial collectives. In 3D environments, the ECM plays a critical role in cancer invasion (Beunk et al. 2023), with high ECM stiffness promoting a jammed state by acting as a rigid barrier that restricts cell migration, and low ECM stiffness allowing cells to rearrange and migrate more freely, leading to an unjammed state.

A signature of the jamming transition is the shift from solid-like to fluid-like behavior, or unjamming, as depicted in a phase diagram. A hypothetical phase diagram proposes physical control parameters for cell jamming: 1/density, 1/cell–cell adhesion, and motility (Figure 1) (Sadati et al. 2013). When cells transition from a static to a motile state, could this process be mapped similarly to the jamming-unjamming transition? What additional biological factors should be considered? The cohesive and coordinated movement of cells during collective migration is implicated in processes such as development, regeneration, and cancer metastasis (Park et al. 2016; Friedl and Gilmour 2009; Wu et al. 2021). While biochemical signaling pathways play a role in regulating cellular dynamics, physical interactions between cells and their environment are also significant determinants of cellular behavior (Trepat et al. 2009; Trepat and Sahai 2018; Jo, Abdi Nansa, and Kim 2020). Living cell dynamics are also constrained by jamming factors described for granular materials, including volume exclusion, size, deformability, crowding, caging, adhesiveness, and stretch/shear forces (Sadati et al. 2013). When cells are sparse, they behave like a fluid, but as they proliferate, mutual crowding leads to a slowing down and eventual arrest of cell motion in a dense monolayer (Garcia et al. 2015). As the cell monolayer matures, it undergoes a phase transition from a flowing state to a jammed state. This process plays a critical biological role in the development of tissue elasticity and the formation of protective barriers in epithelial tissue (Lawson-Keister and Manning 2021; Atia et al. 2021). Additionally, in cancer, jamming acts as a suppressive mechanism for tumor growth (Blauth et al. 2021; Oswald et al. 2017).

During tumorigenesis, cancer cells begin to proliferate in an uncontrolled manner and form a solid tumor (Blauth et al. 2021). In this case, cells within the core of the tumor experience an increase in cell density. An increase in cell density is a crucial

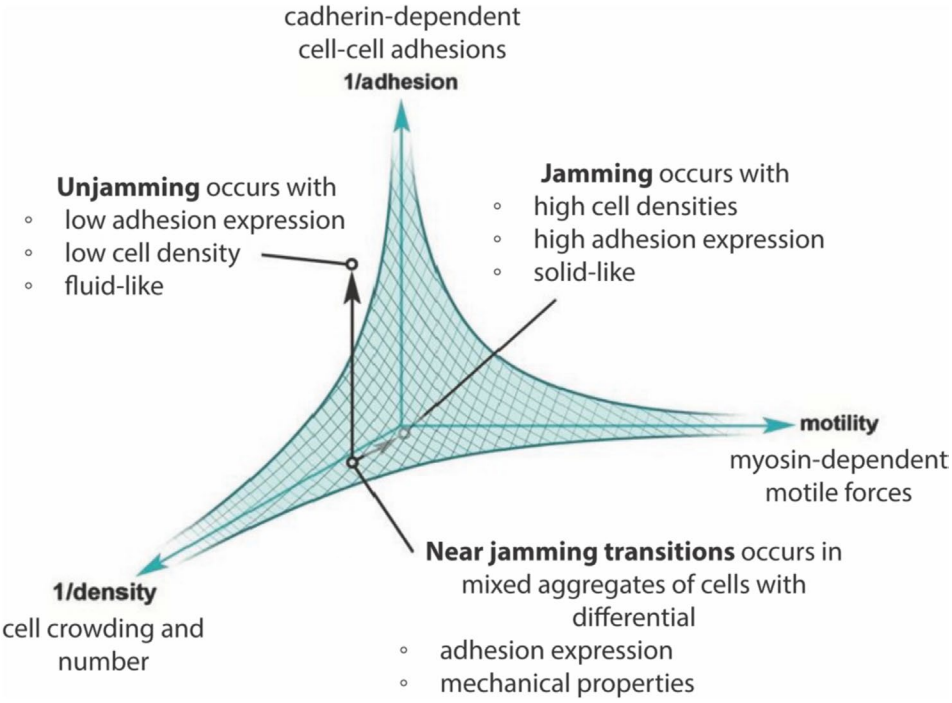

FIGURE 1 | Current understanding of the phase diagram for cell jamming. Higher cell density, stronger cell–cell adhesion, or reduced cell motility results in jamming. The transition towards cell jamming is represented by the shaded region. Near the jamming transition, cells form larger and slower clusters with increasing density as they approach the jammed state. Modified from Reference (Sadati et al. 2013).

contributing factor among the various routes to cell jamming (Lawson-Keister and Manning 2021; Sadati et al. 2013), and the jamming transition occurs at a packing density of one for a 2D cellular system at confluence (Oswald et al. 2017). When the packing density reaches one, cells are densely packed and occupy all available space within a tissue, and further compression requires substantial external force. Experimental observations of cell jamming in human bronchial epithelial cell monolayers involve tracking the evolution of the monolayer in a confined space over time (Garcia et al. 2015). A simple method to reduce cell density is to create a wound, which allows cells at the boundary of the wound to invade and, consequently, prompts the jammed monolayer to rapidly revert to a flowing state (Chepizhko et al. 2018). Wound-induced unjamming transitions have been observed in various cell types, including epithelial, endothelial, and cancer cells (Atia et al. 2021). The mechanical properties of cells also influence the jamming transition in solid tumors.

2.2 | Tumor Cell Mechanical Properties Result in Regions of Jammed Cells Surrounded by Unjammed Cells

When considering cellular transitions from a jammed to an unjammed state, it is essential to evaluate the mechanical properties of cancer cells and how these properties influence the transition. It is well-known that many tumors are rigid masses that are significantly stiffer than their surrounding tissue (Gensbittel et al. 2021; Egeblad, Nakasone, and Werb 2010; Nia, Munn, and Jain 1979). Breast tumors are typically composed of cancer cell clusters ensconced within a stiff stromal environment characterized by excessive deposition of ECM—a strong tumor promoter (Henke, Nandigama, and Ergün 2019). Interestingly, soft cancer cells, which are softer than normal epithelial cells, reside within rigid tumors (Fuhs et al. 2022; Lee and Liu 2015). Primary tumors, from the scale of tissues to individual cells, possess high mechanical heterogeneity (Dagogo-Jack and Shaw 2017; Fisher, Pusztai, and Swanton 2013; Bao et al. 2023). A wide range of cell stiffness exists in tumors, ranging from very stiff cells to cells softer than those found in healthy tissue (Fuhs et al. 2022). Notably, tumors tend to harbor a larger fraction of softer cancer cells, which are more likely to undergo pronounced shifts in membrane tension and are more susceptible to deformation under a given compressive stress. In noncancerous systems, this mechanical softness can increase endocytosis and the turnover of membrane proteins (Tan, Heureaux, and Liu 2015; Willy et al. 2017). Cell stiffness has been linked to E-cadherin turnover in tissues (Willy et al. 2017; Wu et al. 2017) and secretory cells (Willy et al. 2017; Wu et al. 2017), where the effect of cell mechanics on membrane trafficking potentially contributes to fluctuations in cell surface E-cadherin levels within breast epithelial cell monolayers (Cai et al. 2022, 2024) and 3D aggregates (Cai et al. 2022, 2024) in response to mechanical stimuli. Intriguingly, applying mechanical load can engender disparate responses across cells of varying stiffness, even within the confines of the same tissue or tumor (Janmey, Fletcher, and Reinhart-King 2020). As a result, fluidization of certain regions can occur while other areas of the collective remain solid-like, like the behavior observed in granular materials.

Clinical studies have demonstrated that reduced E-cadherin expression within metastatic breast tumors in mice triggers detachment at the single-cell level yet is not sufficient to enhance distant metastasis (Ilina et al. 2020). However, cell rearrangement based on their mechanical properties provides cancer cells an efficient way of relocating towards the tumor periphery. Within tumors, cells of similar stiffnesses tend to congregate, giving rise to distinctive mechanical niches marked by clusters of stiff cells enveloped by softer cells (Fuhs et al. 2022; Baker et al. 2010; Sauer et al. 2023). These clusters of rigid cells within tumors contribute to tumor heterogeneity and influence the metastatic potential of tumor cells since softer cancer cells may be more adept at invading the ECM. At the tumor boundary, cancer cells gain greater access to essential nutrients and secrete matrix metalloproteases (MMPs) to remodel the surrounding matrix, increasing their potential for invasion and dissemination. Furthermore, the inherent resistance of stiffer cells to mechanical forces could potentially drive the selective migration or unjamming of softer cancer cells.

2.3 | From Cell Sorting to Cancer Cell Invasion

If softer cancer cells tend to cluster around stiffer, wild-type cells, this sorting behavior may allow cancer cells to gain better access to factors that promote metastatic potential. How does cell sorting function in the context of the unjamming transition? Cell sorting refers to the spatial organization of cells based on their adhesive and mechanical properties (Skamrahl et al. 2023) (Figure 2). According to the differential adhesion hypothesis (DAH), cells behave dynamically like a fluid, where cells with higher adhesion tend to aggregate together and become surrounded by cells with weaker adhesion (Foty and Steinberg 2005; Steinberg 2007; Tsai, Garner, and Megason 2022; Wu, Yamada, and Wang 2023). The latter cells are more likely to segregate or form separate clusters, while the highly adhesive cells preferentially adhere to each other. The final sorted state corresponds to an equilibrium thermodynamic state with minimum free energy (Foty and Steinberg 2005). An extension of the DAH is the differential interfacial tension hypothesis (DITH), which states that differential adhesion, together with differences in cortical tension due to actomyosin contractility, can predict sorting behavior in 3D mixed-cancer cell spheroids (Pawlizak et al. 2015). When considering surface tension of cells, the plasma membrane and actin cortex can be described by their distinct tension or the measure of the energetic cost of an increase in area for each (Sitarska and Diz-Muñoz 2020; Diz-Muñoz, Fletcher, and Weiner 2013) In multicellular aggregates, tissue surface tension also depends on the energy from cell–cell adhesion and the tension generated by the cellular cortex. Cell–cell adhesion strength, cortical tension, and physical changes in the surface area of a tissue collectively determine surface tension (Pajic-Lijakovic et al. 2023). Additionally, cell stiffness and contractility can lead to sorting, with stiffer and more contractile cells congregating in clusters and displacing softer cells, such as reported for MDCKII cells (Fuhs et al. 2022; Skamrahl et al. 2023) and cancer cells (Fuhs et al. 2022; Skamrahl et al. 2023). The dynamic nature of tissue surface tension, which varies over time, plays a crucial role in patterning

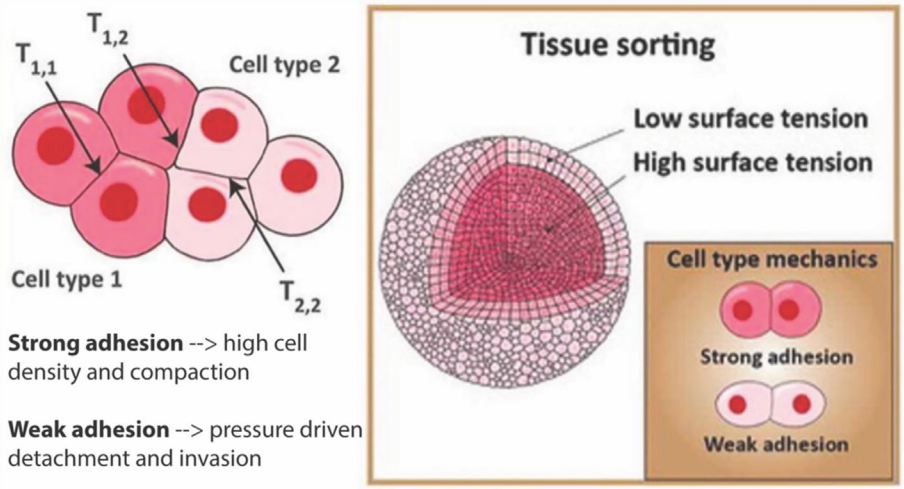

FIGURE 2 | Differential cell adhesions and surface tension in multicellular aggregates prime cancer cells for unjamming transitions. Left panel: Schematic of contact tension in tissues, showing differences in homotypic tensions $T_{1,1}$ and $T_{2,2}$ and heterotypic tension $T_{1,2}$. Right panel: Tissue spreading is governed by relative surface tensions influenced by differences in cell adhesion, with lower surface tension tissues enveloping those with higher surface tension. Modified from Reference (Boot, Koenderink, and Boukany 2021).

involved in cancer progression (Nagle et al. 2022; Heer and Martin 2017) and tissue development (Nagle et al. 2022; Heer and Martin 2017).

The sorting of epithelial and cancer subpopulations within co-culture spheroids is influenced by three key factors: epithelial surface tension, cancer surface tension, and the interfacial tension between epithelial and cancer cells (Pajic-Lijakovic et al. 2023; Nagle et al. 2022). High epithelial surface tension typically fosters a compact and cohesive spheroid structure (Heer and Martin 2017). The level of interfacial tension plays a pivotal role: high interfacial tension leads to the segregation of the two cell types, whereas low interfacial tension promotes mixing in different vertebrate tissue cell types and zebrafish germ layers (Méhes et al. 2023). The strength of these adhesive interactions influences the cohesion among epithelial cells, the ability of lower adhesion cells to integrate with or segregate from the epithelial population, and the extent to which the two cell types can mix (Skamrahl et al. 2023). This balance of surface tensions can create distinct regions within the spheroid, reflecting the complex heterogeneity of the TME.

The invasion of cancer cells from the primary tumor into the surrounding ECM is governed by a complex interplay of forces, including cell–cell surface tension, cell-ECM surface tension, and cell-matrix interfacial tension (Nagle et al. 2022). Cell–cell surface tension determines the structural integrity and shape of the tumor. High surface tension leads to a more compact and less invasive tumor, whereas low surface tension promotes the detachment of cancer cells, thereby facilitating invasion. Specially, loss of a metastatic suppressor gene, NME1 and NME2, decreases surface tension, E-cadherin surface expression, and aggregate size (Nagle et al. 2022; Huna et al. 2021). The composition, density, and organization of the ECM determine its surface tension, which can either inhibit or promote cancer cell invasion (Henke, Nandigama, and Ergün 2019). Increases in collagen deposition and stromal density (jamming) of human breast tumors are correlated with high ECM stiffness (Acerbi et al. 2015). Moreover, cell-matrix interfacial tension—referring to the tension at the interface between the tumor and the ECM—determines the ability of invading cells to adhere to and invade the surrounding matrix (Franchi, Kyriakopoulou, and Mierke 2024). Here, we are considering the tension generated between focal adhesions and the ECM, along with tension and strain generated between adherens junctions. High interfacial tension generally serves as a barrier to invasion or jamming, whereas low interfacial tension supports the invasion or unjamming of cancer cells into the ECM. Additionally, variations in the mechanical properties of the ECM across different regions, modeled computationally, can generate a gradient in cell-matrix interfacial tension, directing cancer cells towards regions of lower interfacial tension, in this case (Pajic-Lijakovic et al. 2023). This directional migration, unjamming cells away from jammed cells within the tumor, highlights the importance of mechanical and structural properties of the tumor and surrounding ECM in determining the invasive potential of tumors.

The physical properties of tumor cells are a factor in the regulation of the spatial arrangement of cells. This has a critical impact on unjamming transitions, especially in fibrous 3D matrices, where physical barriers and chemoattractant gradients become more complex. Generally, individual cells may invade using mesenchymal or amoeboid migration, groups of sorted cells can collectively invade by maintaining strong cell–cell adhesions (Kabla 2012). Cancer cell migration is a key element of the invasion-metastasis cascade, where invasive cells secrete matrix-degrading enzymes and extend protrusions to promote migration (Krause and Wolf 2015; Caswell and Zech 2018). In soft collagen matrices, cancer aggregates have been observed to display increased pressure within the aggregate due to cell swelling caused by the matrix's insufficient mechanical feedback in response to cell pulling forces (Raghuraman et al. 2022). In cancer metastasis, pressure within the tumor can cause cells to unjam or break away from the primary tumor and invade surrounding tissues (Purkayastha, Jaiswal, and Lele 2021). Understanding the physical and biochemical mechanisms

underlying cell sorting and unjamming transitions is crucial for inhibiting invasive behaviors that lead to tumor cell migration.

While 2D cell migration generally involves lamellipodial or filopodial protrusions at the leading edge and the formation of focal adhesions, migration modes in 3D environments can vary significantly based on the mechanical properties of the surrounding ECM. Migration through 3D environments and in the context of metastasis, presents challenges as cancer cells must navigate dense and complex ECMs, requiring them to adapt to the mechanical properties of the matrix through remodeling or degradation (Yamada and Sixt 2019; Merino-Casallo et al. 2022; Krause and Wolf 2015). In such environments, interactions between neighboring cells and the surrounding matrix are increased. For collective migration, cells need to maintain interactions with the surrounding tissue as well as other cells in a group (Merino-Casallo et al. 2022; Gjorevski et al. 2015). Various modes of migration are observed in 3D settings, including mesenchymal, amoeboid, and lobopodial migration (Driscoll and Danuser 2015; Petrie and Yamada 2016; Pawluchin and Galic 2022).

2.4 | Cells Undergo Various Modes of 3D Cell Migration

How do unjamming phenotypes fit into our current understanding of cell migration, especially given the variety of migration modes cells can undergo? Different modes of cell migration are triggered or defined by distinct biochemical and biophysical mechanisms. For instance, mesenchymal migration is characterized by elongated cell morphology and is commonly observed during development and tissue repair. Cells use actin polymerization to generate lamellipodia or filopodia that protrude at the leading edge and secrete proteolytic enzymes such as MMPs to remodel the ECM, creating paths for migration (Caswell and Zech 2018; Driscoll and Danuser 2015). Cancer cells typically adhere to and move along ECM fibers, such as collagen and fibronectin, and exhibit front-rear polarity, with the cell moving forward by contracting its rear end and pulling itself in the direction of migration (Krause and Wolf 2015).

Amoeboid migration, on the other hand, is faster, lacks prominent protrusions, and involves minimal proteolytic degradation (Lämmermann and Sixt 2009; Graziani et al. 2022). Rapidly moving amoeboid cells, including neutrophils, macrophages, and invasive cancer cells, are highly deformable and unjamming can occur with the path of least resistance in terms of durotaxis and ECM pore size (Vesperini et al. 2021). Here, cells possess a rounded morphology, exhibit weak adhesions, and use actomyosin contractility to generate the force to squeeze through ECM pores of ideal size (Van Helvert, Storm, and Friedl 2017). Actin protrusions or hydrostatic membrane blebs drive deformations of cell shape and push the cell forward (Caswell and Zech 2018). Cancer cells often use amoeboid migration to infiltrate surrounding tissues and metastasize to distant sites (Paňková et al. 2010; George et al. 2023). Associated with amoeboid movement, lobopodia are blunt cylindrical protrusions that extend from the leading edge of a migrating cell and are driven by intracellular pressure (Petrie and Yamada 2012; Bodor et al. 2020). Migration in this mode is driven by the assembly of actin filaments at the leading edge, which adheres to the ECM and provides traction for forward movement, while actin filaments at the rear of the cell disassemble. In 3D environments, fibroblasts (Petrie et al. 2012; Wu, Gilkes, and Wirtz 2016) and other cell types tend to utilize lobopodia instead of lamellipodia and filopodia commonly observed in 2D settings (Petrie et al. 2012; Wu, Gilkes, and Wirtz 2016).

Cells can switch between the different modes of migration depending on the cell type, the properties of the surrounding ECM, and biochemical signaling cues. For instance, cancer cells can switch between migration modes in response to protease inhibition, viscoelastic properties, adhesion strength, and confinement level (Paňková et al. 2010; Khoo et al. 2019). Understanding these diverse migration modes and their regulation is essential for gaining insights into cancer progression.

2.5 | Unjamming Transition Versus EMT in Signaling a Motile State

Unjamming is thought to be a distinct process from motility induction driven by factors such as chemoattractants, electrical currents, or wound formation (Atia et al. 2021). In situations where cells are confined and densely packed, such as in tumors, they may undergo different modes of migration in response to physical forces exerted on the cells by the tissue microenvironment (Gensbittel et al. 2021; Baghban et al. 2020; Cai et al. 2024; Yamaguchi, Wyckoff, and Condeelis 2005; Polacheck, Zervantonakis, and Kamm 2013; Pastushenko and Blanpain 2019; Jain, Martin, and Stylianopoulos 2014; Almagro et al. 2022; Winkler et al. 2020). The transition from a static to a motile state has been investigated primarily from the EMT paradigm, where epithelial cells, solid-like tissue, lose cell polarity, cell–cell adhesions, and acquire invasive properties undergo tissue fluidization (Figure 3) (Yamada and Sixt 2019; Pastushenko and Blanpain 2019; Campbell and Casanova 2016; Nieto et al. 2016). Epithelial migration is characterized by strong cell–cell junctions (high E-cadherin and low vimentin expression), and focal adhesions, while mesenchymal migration involves weak cell–cell adhesions (low E-cadherin, high N-cadherin, high vimentin expression), and decreased focal adhesions in follower cells (Nieto et al. 2016). Studies have found that applying compressive stress to a monolayer of primary human bronchial epithelial cells stimulates a jammed-to-unjammed transition, which is not primarily driven by EMT (Park et al. 2015; Mitchel et al. 2020). This indicates a potential distinct nature of the unjamming transition.

Epithelial and mesenchymal cells display contrasting collective behaviors. Epithelial cells, when packed in position, lack the energy to overcome high junctional tension (Figure 3A) (Yamada and Sixt 2019; Park et al. 2015; Palamidessi et al. 2019). Unjamming can occur when tension or confinement is reduced and cell adhesion is high, resulting in a tightly bound group where all cells contribute equally to collective movement (Figure 3B) (Cai et al. 2024; Ilina et al. 2020). On the other hand, mesenchymal cells migrate as a loosely connected pack, resembling collective motion of animals, bacteria, and self-propelled particles (Figure 3C) (Shellard and Mayor 2020). During EMT, intercellular adhesions weaken, and epithelial adhesion markers such

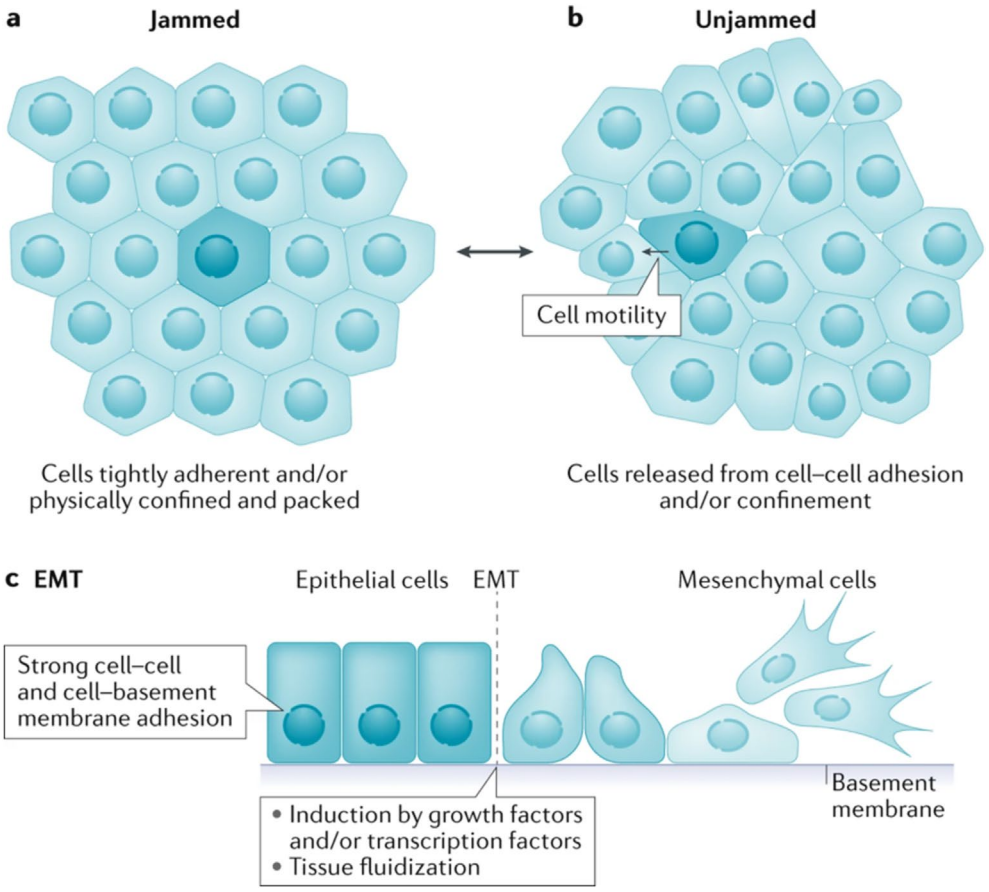

FIGURE 3 | Unjamming transition and EMT models for collective tumor cell migration. Schematic of the transition between (A) jammed and (B) unjammed states for epithelial cell sheets. Here, nonmotile cells are jammed, and motile cells are unjammed. (C) Schematic of the EMT model for collective cell migration. Adapted from Reference (Yamada and Sixt 2019).

as E-cadherin are replaced by the upregulation of N-cadherin. Leader cells maintain strong focal adhesions, while follower cells experience weakened adhesions and reduced traction forces (Campbell and Casanova 2016). In contrast, unjammed bronchial epithelial cells undergoing collective motion maintain strong cell–cell junctions while exhibiting fluid-like behavior characterized by elongated cell shapes (Mitchel et al. 2020).

Traditionally, the unjamming transition and EMT have been regarded as distinct processes, but could they be linked in certain contexts? EMT is no longer viewed as a single, binary process; rather it encompasses a spectrum of overlapping biological characteristics. RNA and protein profiling studies suggest that cells can adopt intermediate states or undergo partial EMT, better termed as epithelial-mesenchymal plasticity (EMP) (Haerinck, Goossens, and Berx 2023; Yang et al. 2020). EMP describes the ability of cells to move readily between epithelial- and mesenchymal-like states, primarily regulated by EMT-transcription factors (EMT-TFs). Notably, EMT-TFs are also expressed in nonepithelial cell types, adding complexity to the traditional understanding of EMT (Yang et al. 2020). Interestingly, it has been reported that cancer stemness, cell survival, metabolic changes, and resistance to anticancer therapeutic drugs can arise from EMT-TFs (Yang et al. 2020; Goossens et al. 2017). In addition, the loss of the metastatic suppressor gene, NME1, in epithelial cancer cells results in a hybrid intermediate phenotype due to altered cadherin expression (Huna et al. 2021) and low surface tension (Nagle et al. 2022). These factors associated with EMT-TFs and genes are also promoted in high matrix stiffness environments during jamming/unjamming transitions.

Our recent work investigating multicellular sorting and migration under confinement demonstrates that partial EMT (characterized by low E-cadherin expression and high vimentin expression) combined with reduced matrix stiffness can lead to burst-like migration of human breast cancer and benign cells (Cai et al. 2024). This burst-like migration occurs only after confinement is released, indicating that EMP and the unjamming transition may be coupled in specific contexts. Another recent study also reported that cancer cell spheroids exhibit solid-like behavior in small-pore hydrogels, compared with more gas-like behavior in large-pore hydrogels (Van Der Net et al. 2024). Furthermore, this work showed that EMT and unjamming are linked to the expression of MMPs, which assist in degradation of the ECM, enhancing cell motility. Continued research into the coupling of EMT and unjamming transitions is warranted, both in cancer and noncancer systems.

It is therefore proposed that at the primary tumor site, a leader cell, surrounded by solid tissues, is triggered to transition from a solid-like, jammed phase to a fluid-like, motile state (Haeger et al. 2014; Park et al. 2016). Not only do cell–cell interactions within the tumor regulate the unjamming transition, but

interactions between the cells and the ECM also play a role (Saraswathibhatla, Indana, and Chaudhuri 2023; Eble and Niland 2019).

3 | Cell-ECM Mechanotransduction Supports Tumor Cell Migration and Cancer Progression by Promoting Unjamming Transitions

Up to this point, we have focused on the influence of cell–cell interactions in the jamming transition during cancer cell invasion. However, once cancer cells leave the primary tumor site, their interactions with the surrounding environment, shaped by various biochemical and physical characteristics, can further promote metastatic behavior. The TME is a complex system composed of diverse cellular and extracellular components, including tumor cells, stromal cells, immune cells, carcinoma-associated fibroblasts, and non-cellular components within the ECM (Baghban et al. 2020; Polacheck, Zervantonakis, and Kamm 2013; Zhou et al. 2022). In addition to biochemical signals, physical cues from the microenvironment can significantly impact cell proliferation, migration, and metastatic potential (Zhou et al. 2022; Salvatore et al. 2017; Wang et al. 2020). The ability of cells to migrate collectively is influenced by microenvironmental conditions, such as cell density and ECM properties. Tumors are often stiffer than normal tissue due to increased concentrations of ECM components such as collagen and fibronectin (Henke, Nandigama, and Ergün 2019). Mechanical inputs, such as ECM stiffness or interstitial pressure, and mechanical forces, including tension and compression, have been shown to modulate cancer cell metabolism, proliferation, migration, and stemness (Saraswathibhatla, Indana, and Chaudhuri 2023; Henke, Nandigama, and Ergün 2019; Pickup, Mouw, and Weaver 2014; Nguyen et al. 2022) (Figure 4). This process of cells sensing and responding to the ECM is referred to as cell-ECM mechanotransduction.

In 3D environments, cells encounter various degrees of physical confinement in tissues, as well as mechanical forces including compressive and shear stresses during both single and collective cell migration (Jain, Martin, and Stylianopoulos 2014). High mechanical stress in tumors can prompt metabolic changes to cancer cells to acquire stem-like cell properties, driving tumor progression and promoting metastasis (Liu et al. 2020). The mechanical properties of the TME, such as solid stress, matrix stiffness, and interstitial fluid flow, change as tumor growth and development occur. Compressive stress in human tumors can reach levels of 35–142 mmHg, impacting cancer cells and surrounding blood and lymphatic vessels (Liu et al. 2020).

Beyond mechanical stress, ECM stiffness and the physical confinement of tumor cells within the microenvironment also play critical roles in influencing the unjamming transition. This raises important questions: How does a cell's response to its mechanical environment trigger transitions between jamming and unjamming? Can physical confinement caused by ECM

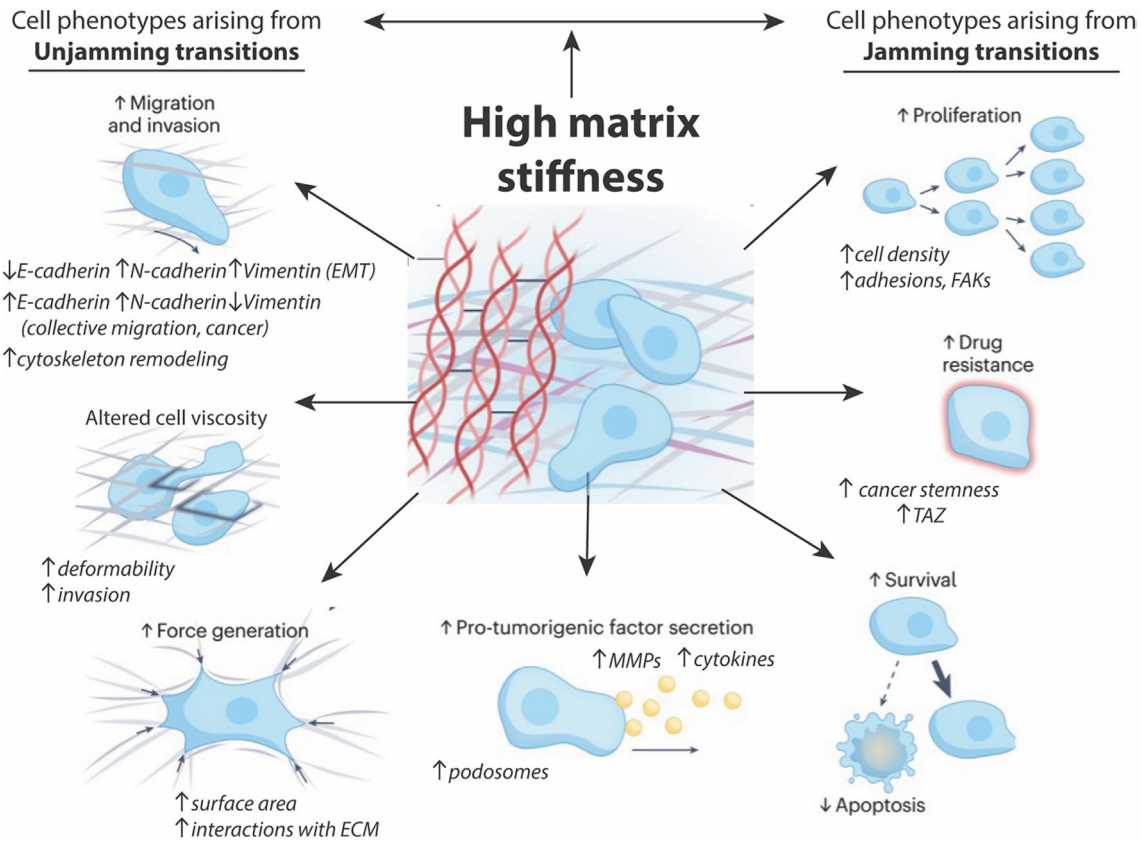

FIGURE 4 | Unjamming and jamming transitions in response to high matrix stiffness environments. Tumor cell adaptations resulting from high matrix stiffness during primary tumor development can give rise to jamming and unjamming transitions. Modified from Reference (Cambria et al. 2024).

stiffness "jam" cells and hinder metastasis? Or do cancer cell mechanics enable them to adapt and navigate stiff ECM more efficiently, promoting unjamming? In the next section, we will delve into how cell-ECM interactions drive unjamming transitions and speculate on the potential role of mechanosensitive channels and transcription factors in mediating the unjamming transition.

3.1 | Matrix Stiffness and Physical Confinement Guide Unjamming Transitions

The cellular ECM is a complex network of proteins and fibers, including collagen, elastin, and fibronectin, with mechanical properties that vary depending on tissue type (Cox 2021; Chaudhuri et al. 2020). Mechanosensitive proteins such as integrins and focal adhesion kinase play a crucial role in converting mechanical signals from the cellular microenvironment into biochemical cues that guide cell migration (Guan 1997; Chen et al. 2017). Of particular significance is the impact of changes in matrix stiffness on cell behavior and migration, mediated through mechanotransduction pathways and signaling mechanisms. Notably, breast cancer tissue is significantly stiffer (~4 kPa) than normal breast tissue (~0.2 kPa), emphasizing the role of mechanical cues in cancer progression (Paszek et al. 2005; Xu et al. 2023). Studies have shown that cells cultured on stiffer substrates exhibit an elongated morphology, increased spreading, and faster migration due to enhanced contractile forces generated on rigid surfaces (Janmey, Fletcher, and Reinhart-King 2020). In high-stiffness matrix environments, cancer cells generate increased 3D traction forces (Afthinos et al. 2022). These cells establish stronger cell-ECM adhesions and traction forces, enabling more rapid and efficient migration.

Primary tumors are encapsulated within a basement membrane and are subject to increased confinement stress as they grow, leading to a buildup of internal pressure driven by cell proliferation (Cai et al. 2024; Yan et al. 2021). Recent work demonstrates how high pressure within a spheroid can result in spontaneous burst-like motility of tumor cells that effectively disrupts the cell jamming that typifies high cell density within the spheroid core (Cai et al. 2024; Raghuraman et al. 2022). This burst-like migration, driven by the pressure difference between the spheroid and the degraded ECM, allows cancer cells to gain access to distant sites of metastasis. Here, burst-like migration refers to the sudden, collective movement of cells from a multicellular aggregate into the surrounding matrix, resembling a "burst." This phenomenon exemplifies an unjamming transition in a 3D context.

Cell sorting within 3D multicellular aggregates contributes to heterogeneity, potentially creating gradients of mechanical stress and cell–cell interactions that drive transitions between jammed and unjammed states (Han, Kwon, and Kim 2021). During burst-like migration observed in an epithelial and cancer co-culture spheroid model (Cai et al. 2024), the cells initially exist in a jammed state, characterized by dense packing and low motility. Triggered by changes in the confinement by the surrounding matrix, the cells rapidly transition to a state of high motility, enabling collective invasion into the ECM. During this process, cells overcome mechanical constraints imposed by both neighboring cells and the ECM.

Burst-like migration occurs mostly in the form of cellular aggregates rather than individual cells, increasing the potential for micrometastasis (Raghuraman et al. 2022). This involves tumor cell clusters traveling to distant sites within the body where they establish small secondary tumors. However, a stiff ECM can also impede or jam individual cells. As individual cancer cells navigate the surrounding matrix, they can encounter constraints such as the dense ECM and physical obstacles, resulting in slow and inefficient migration. This impediment can result in jamming of individual cells; while collectively migrating cells are more likely to unjam, a behavior that is more commonly associated with successful metastatic progression.

ECM stiffening is driven by the excessive activity of proteins and enzymes, leading to crosslinking of collagen fibers and other ECM components (Winkler et al. 2020; Lu et al. 2011; Bonnans, Chou, and Werb 2014). In the context of confined 3D cancer cell migration, cells can actively remodel and degrade the surrounding matrix to create migration pathways (Krause and Wolf 2015; Lu et al. 2011). The stiffness and porosity of the ECM influence the degree of physical confinement experienced by cells. In response to different levels of confinement, cancer cells may switch their migration mode between mesenchymal and amoeboid migration (Paňková et al. 2010; Khoo et al. 2019). Amoeboid migration is favored when navigating tight gaps in dense tissues, whereas mesenchymal migration is typically employed in less dense environments. Moreover, increased physical confinement stemming from high matrix stiffness can result in cell nucleus deformation, leading to changes in cancer cell polarity and gene expression (Krause and Wolf 2015).

The ECM is not merely a rigid, crosslinked network of fibers but also behaves as a viscoelastic material, influencing the migration of tumor cells (Chaudhuri et al. 2020; Saraswathibhatla, Indana, and Chaudhuri 2023). A recent study found that extracellular fluid viscosity can promote cancer cell migration by increasing the density of the cortical actin network (Bera et al. 2022). This alteration in cortical actin promotes cell swelling and increased membrane tension, mediating calcium influx and increased RhoA-dependent actin contractility (Bera et al. 2022). In this case, myosin-dependent motility and intracellular pressure increase, resulting in an unjamming transition. Additionally, the plastic deformation of the ECM contributes to the ability of cellular forces to remodel collagen fibers (Schultz, Kyburz, and Anseth 2015; Ban et al. 2018; Malandrino et al. 2019). Studies demonstrate that cells can physically reorganize ECM networks, in addition to their ability to degrade the network through the release of enzymes, to better navigate through the ECM. In ECMs with higher plasticity, cancer and stem cells can create microchannels within the ECM to facilitate their motility, whereas more elastic ECMs tended to impede migration. In one study, mesenchymal stem cells promoted nuclear piston-driven protrusion expansion linked to the activation of mechanosensitive ion channels, resulting in an increase in protrusion osmotic pressure (Lee et al. 2021). These findings can be related to the jamming transition, where higher ECM plasticity promotes the unjamming of cancer cells in a physical context. This illustrates

how cells can sense and manipulate extracellular properties to promote their motility through the ECM (Chaudhuri et al. 2020).

Questions remain about how the viscoelastic properties of cancer cells feedback into their ability to undergo more persistent motility. When cells undergo relaxation or unjamming, they collectively act as a viscoelastic fluid, whereas the jammed phenotype can be considered a viscoelastic solid. Recent studies using atomic force microscopy and micropipette aspiration have reported that single cancer cells are more deformable, behaving more fluid-like and demonstrating lower apparent viscoelasticity than normal cells (Xie et al. 2019; Mierke 2021; Nematbakhsh, Pang, and Lim 2017). Here, it is proposed that the decreased viscoelasticity of cancer cells, attributed to actin cytoskeleton reorganization, leads to enhanced motility (Nematbakhsh, Pang, and Lim 2017). A study characterizing viscoelastic creep behavior in mouse fibroblasts and human embryonic spheroids further indicates that tissue relaxation following micropipette aspiration is deformation-dependent (Boot et al. 2024). Furthermore, the interplay between the viscoelastic properties of cancer cells and the ECM, and how they influence each other, has yet to be fully explored. Further investigation is warranted to better understand the role of viscoelasticity in the unjamming transition, where advances in tissue engineering are necessary (Guimarães et al. 2020; Curvello et al. 2023; Ligorio and Mata 2023).

3.2 | Regulation of Mechanosensitive Ion Channels and Transcription Factors in Unjamming Transitions

How might distinct biomechanical cues from the ECM regulate signaling in 3D cell migration? Cells encounter tensile stretch as they navigate through constrained spaces, such as narrow channels and dense ECM environments (Gjorevski et al. 2015). During invasion through the ECM and processes such as intravasation and extravasation, migrating cells experience compression due to constricted pathways (Pickup, Mouw, and Weaver 2014; Heureaux-Torres et al. 2018). In response to these physical limitations, cells generate forces to deform their shapes to squeeze through narrow passages, enabling migration within confined 3D regions. Jamming transitions during 3D confined migration offer insights into the mechanisms through which cells can become trapped during migration in the primary tumor or in attempts to invade into the ECM (Haeger et al. 2014; Ilina et al. 2020). As cells navigate tight spaces within the dense ECM, they encounter increased mechanical resistance. Cell motion can be hindered if the mechanical forces exerted by the cells exceed a certain threshold, and the cells can become immobilized, or jammed (Janmey, Fletcher, and Reinhart-King 2020).

Mechanical stimuli have been shown to reshape epithelial cell–cell junctions through the elongation and contraction of junctions via mechanosensitive channels (Varadarajan et al. 2022). However, the precise molecular mechanisms that translate mechanical cues into changes in invasive behavior remain poorly understood. Earlier work from our lab revealed that the exogenous expression of the mechanosensitive channel of large conductance (MscL) in cancer cells inhibits cell entry into narrow 3D channels (Heureaux-Torres et al. 2018). Another mechanosensitive channel of particular interest is Piezo1.

Piezo1 regulates cell proliferation and migration in response to various mechanical stimuli and mediates cell motility in both individual and collective migration (Gudipaty et al. 2017; Yu et al. 2020; Li et al. 2015; Holt et al. 2021; Murthy, Dubin, and Patapoutian 2017). Importantly, Piezo1 has been shown to be upregulated in most cancers and is associated with unfavorable prognosis (Li et al. 2015, 2022; Dombroski et al. 2021). In tumor cell migration, Piezo1 activation enhances the ability of cancer cells to migrate under compressive stress and through tight spaces by inducing a switch from F-actin–driven pseudopods to bleb-driven motility (Dombroski et al. 2021; Srivastava et al. 2020). Recent work from our lab and others demonstrates that mechanical activation of Piezo1 leads to enhanced matrix degradation, actin protrusion formation, and an influx of calcium ions (Luo et al. 2022; Grannemann et al. 2023). Given that Piezo channels are tethered to the actin cytoskeleton through the cadherin-β-catenin complex (Wang et al. 2022), Piezo1 and E-cadherin may work together to transmit adhesion-cytoskeleton forces. A compelling aspect is the potential involvement of Piezo1 mechanotransduction in the regulation of E-cadherin expression due to the role of Piezo1 in transducing mechanical forces applied externally and internally at the plasma membrane (Li et al. 2015). A recent study from our group demonstrated that cell sorting and burst-like migration resulting from ECM stiffness is E-cadherin dependent, supporting Piezo1 activity in tumor cell migration (Cai et al. 2024). As a result, the influence of mechanosensitive channels potentially extends to governing E-cadherin turnover, thereby linking mechanotransduction and cellular adhesion dynamics, potentially as a mechanism for the unjamming transitions.

Furthermore, mechanosensitive transcription activators, YAP and TAZ, are implicated in altering cellular adhesion dynamics and transcription factor expression, which are upregulated in several cancers (Zanconato, Cordenonsi, and Piccolo 2019). YAP and TAZ were first identified as important genes in the Hippo pathway, a conserved signaling pathway involved in organ development (Boopathy and Hong 2019; Zheng and Pan 2019). With respect to cell migration, YAP/TAZ are well understood to regulate actin cytoskeleton rearrangement and focal adhesion maturation, enabling persistent motility (Zanconato, Cordenonsi, and Piccolo 2019; Qiao et al. 2017; Mason et al. 2019). Beyond biochemical signaling, there is overwhelming evidence supporting how YAP and TAZ regulation is heavily influenced by cellular mechanotransduction (Panciera et al. 2017).

Specifically, the localization of YAP changes when subjected to force (Nasrollahi et al. 2017; Panciera et al. 2017; Elosegui-Artola et al. 2017). It is understood that when the nucleus is stretched, such as in the case of cells migrating on a stiff substrate, YAP is activated and localizes to the nucleus (Panciera et al. 2017; Elosegui-Artola et al. 2017). For human breast tumors, YAP nuclear localization increases in high ECM stiffness, along with an increase in pMLC, pFAK, and activated β1 integrin mechanosignaling (Acerbi et al. 2015). Recently, it has been reported that epithelial cells primed on stiff substrates maintain faster motility even when migrating on softer substrates, and this "memory" is YAP-dependent (Nasrollahi et al. 2017). It is also suggested that YAP localization to the nucleus is due primarily to nuclear compression rather than substrate stiffness alone (Koushki et al. 2023). When tumor cells migrate through

confined spaces in stiff ECMs, not only do cells sense stiffer substrates, but the nucleus also deforms, such as with the formation of a nuclear piston (Lee et al. 2021), to facilitate migration through confinement. Whether substrate-induced nuclear deformation alone or in combination with other mechanisms for nuclear stretching leads to a transition to an unjammed state remains to be investigated.

4 | Conclusions and Future Perspectives

Tumor cell migration is a complex phenomenon due to the heterogeneity of the TME and involves multi-mode migration, which makes treating metastatic cancers challenging. Within the tumor, different cell types reside and congregate based on cell–cell mechanical interactions, such as cell adhesiveness and stiffness. Furthermore, tumor cells interact with the surrounding ECM, where ECM stiffness and viscoelasticity can influence gene expression and motility. In addition to the well-understood biochemical signaling of tumor cell invasion, we favor the paradigm of the jamming transition. Here, the mechanical properties of cells drive sorting within the tumor, creating areas of jammed, solid-like cell mass surrounded by unjammed, fluid-like cell motion. Unjammed, fluid-like cells are located at the periphery with better access to the ECM, where they are triggered by and remodel the ECM for more efficient tumor cell migration and ultimate invasion. Future work needs to continue elucidating the molecular mechanisms underlying the unjamming transition to help uncouple the different roles of biochemical and mechanical signaling in tumor cell migration.

In this review, we primarily discussed unjamming transitions regulated by cell–cell interactions within the tumor and cell-ECM interactions. Recently, there has been an increased emphasis on the broader TME and how cooperation among different cell types favors cancer progression (Schulz et al. 2019). Fibroblasts are a dominant cell type within the TME and have a major role in tissue repair (Kalluri 2016; Yang et al. 2023). Cancer-associated fibroblasts (CAFs) are of great interest in cancer biology due to their ability to secrete soluble factors and remodel the ECM, impacting tumor cell behavior, such as those linked with the jamming transitions (Yoshida 2020; Chen, McAndrews, and Kalluri 2021). The remodeling of the ECM by CAFs changes the mechanical properties of the ECM and the resulting forces experienced by tumor cells. CAFs produce collagen, which increases the stiffness of the ECM (Takai et al. 2016), having implications in tumor cell mechanosensing expression (Acerbi et al. 2015). Even more intriguing and novel are the interactions between tumor cells and CAFs, where it has been reported that cancer cells exhibit changes in YAP nuclear localization due to CAF capsules (Barbazan et al. 2023). Here, CAFs induce compressive forces on cancer cells, demonstrating that not only can ECM stiffness influence gene expression, but also forces induced by fibroblasts in the TME. Interestingly, CAF capsules surrounding and applying compressive force on cancer cells in this system were shown to restrain cancer cell growth (Barbazan et al. 2023), potentially leading to a jammed state. This suggests a complex interplay between substrate/cell stiffness and gene expression for inducing or inhibiting tumor cell migration. Despite this, it remains unclear how interactions with other cell types within the TME directly lead to unjamming transitions in cancer cell progression. Innovations in long-term, high-resolution imaging, 3D tumor cell models, multi-scale computational models, and the engineering of more complex TMEs will assist in the effort to understand the molecular mechanisms underlying the unjamming paradigm in tumor cell migration.

Author Contributions

G.C. and A.P.L. conceived the review. G.C. and N.C.R. drafted the review. All authors edited the review and approved the review.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

Acerbi, I., L. Cassereau, I. Dean, et al. 2015. "Human Breast Cancer Invasion and Aggression Correlates With ECM Stiffening and Immune Cell Infiltration." *Integrative Biology* 7: 1120–1134.

Afthinos, A., K. Bera, J. Chen, et al. 2022. "Migration and 3D Traction Force Measurements Inside Compliant Microchannels." *Nano Letters* 2022: 7327.

Almagro, J., H. A. Messal, A. Elosegui-Artola, J. van Rheenen, and A. Behrens. 2022. "Tissue Architecture in Tumor Initiation and Progression." *Trends in Cancer* 8: 494–505.

Atia, L., D. Bi, Y. Sharma, et al. 2018. "Geometric Constraints During Epithelial Jamming." *Nature Physics* 14: 613–620.

Atia, L., J. J. Fredberg, N. S. Gov, and A. F. Pegoraro. 2021. "Are Cell Jamming and Unjamming Essential in Tissue Development?" *Cells and Development* 168: 203727.

Baghban, R., L. Roshangar, R. Jahanban-Esfahlan, et al. 2020. "Tumor Microenvironment Complexity and Therapeutic Implications at a Glance." *Cell Communication and Signaling* 18: 1–19.

Baker, E. L., J. Lu, D. Yu, R. T. Bonnecaze, and M. H. Zaman. 2010. "Cancer Cell Stiffness: Integrated Roles of Three-Dimensional Matrix Stiffness and Transforming Potential." *Biophysical Journal* 99: 2048.

Ban, E., J. M. Franklin, S. Nam, et al. 2018. "Mechanisms of Plastic Deformation in Collagen Networks Induced by Cellular Forces." *Biophysical Journal* 114: 450–461. https://doi.org/10.1016/j.bpj.2017.11.3739.

Bao, L., H. Kong, Y. Ja, et al. 2023. "The Relationship Between Cancer and Biomechanics." *Frontiers in Oncology* 13: 1273154.

Barbazan, J., C. Pérez-González, M. Gómez-González, et al. 2023. "Cancer-Associated Fibroblasts Actively Compress Cancer Cells and Modulate Mechanotransduction." *Nature Communications* 14: 1–17.

Behringer, R. P. 2015. "Jamming in granular materials." *Comptes Rendus Physique* 16: 10–25.

Behringer, R. P., and B. Chakraborty. 2018. "The Physics of Jamming for Granular Materials: A Review." *Reports on Progress in Physics* 82: 012601.

Bera, K., A. Kiepas, I. Godet, et al. 2022. "Extracellular Fluid Viscosity Enhances Cell Migration and Cancer Dissemination." *Nature* 611: 365–373.

Beunk, L., N. Wen, S. van Helvert, et al. 2023. "Cell Jamming in a Collagen-Based Interface Assay Is Tuned by Collagen Density and Proteolysis." *Journal of Cell Science* 136: 1–10.

Bi, D., X. Yang, M. C. Marchetti, and M. L. Manning. 2016. "Motility-Driven Glass and Jamming Transitions in Biological Tissues." *Physical Review X* 6: 021011.

Blauth, E., H. Kubitschke, P. Gottheil, S. Grosser, and J. A. Käs. 2021. "Jamming in Embryogenesis and Cancer Progression." *Frontiers of Physics* 9: 445.

Bodor, D. L., W. Pönisch, R. G. Endres, and E. K. Paluch. 2020. "Of Cell Shapes and Motion: The Physical Basis of Animal Cell Migration." *Developmental Cell* 52: 550–562.

Bonnans, C., J. Chou, and Z. Werb. 2014. "Remodelling the Extracellular Matrix in Development and Disease." *Nature Reviews. Molecular Cell Biology* 15: 786–801.

Boopathy, G. T. K., and W. Hong. 2019. "Role of Hippo Pathway-YAP/TAZ Signaling in Angiogenesis." *Frontiers in Cell and Development Biology* 7: 440860.

Boot, R. C., G. H. Koenderink, and P. E. Boukany. 2021. "Spheroid Mechanics and Implications for Cell Invasion." *Advances in Physics: X* 6: 1–35.

Boot, R. C., A. van der Net, C. Gogou, et al. 2024. "Cell Spheroid Viscoelasticity Is Deformation-Dependent." *Scientific Reports* 14: 1–12.

Brown, E., N. Rodenberg, J. Amend, et al. 2010. "Universal Robotic Gripper Based on the Jamming of Granular Material." *Proceedings of the National Academy of Sciences of the United States of America* 107: 18809–18814.

Cai, G., A. B. Harada, and K. Nordstrom. 2021. "Mesoscale Metrics on Approach to the Clogging Point." *Granular Matter* 23: 1–11.

Cai, G., X. Li, S. S. Lin, et al. 2024. "Matrix Confinement Modulates 3D Spheroid Sorting and Burst-Like Collective Migration." *Acta Biomaterialia* 179: 192–206. https://doi.org/10.1016/j.actbio.2024.03.007.

Cai, G., A. Nguyen, Y. Bashirzadeh, et al. 2022. "Compressive Stress Drives Adhesion-Dependent Unjamming Transitions in Breast Cancer Cell Migration." *Frontiers in Cell and Development Biology* 10: 1983.

Cambria, E., M. F. Coughlin, M. A. Floryan, G. S. Offeddu, S. E. Shelton, and R. D. Kamm. 2024. "Linking Cell Mechanical Memory and Cancer Metastasis." *Nature Reviews Cancer* 2024: 1–13. https://doi.org/10.1038/s41568-023-00656-5.

Campbell, K., and J. Casanova. 2016. "A Common Framework for EMT and Collective Cell Migration." *Development* 143: 4291–4300.

Caswell, P. T., and T. Zech. 2018. "Actin-Based Cell Protrusion in a 3D Matrix." *Trends in Cell Biology* 28: 823–834.

Chang, C. S. 2022. "Jamming Density and Volume-Potential of a Bi-Dispersed Granular System." *Geophysical Research Letters* 49: e2022GL098678.

Chaudhuri, O., J. Cooper-White, P. A. Janmey, D. J. Mooney, and V. B. Shenoy. 2020. "Effects of Extracellular Matrix Viscoelasticity on Cellular Behaviour." *Nature* 584: 535–546.

Chen, Y., L. Ju, M. Rushdi, C. Ge, and C. Zhu. 2017. "Receptor-Mediated Cell Mechanosensing." *Molecular Biology of the Cell* 28: 3134–3155.

Chen, Y., K. M. McAndrews, and R. Kalluri. 2021. "Clinical and Therapeutic Relevance of Cancer-Associated Fibroblasts." *Nature Reviews Clinical Oncology* 18: 792–804.

Chepizhko, O., M. C. Lionetti, C. Malinverno, et al. 2018. "From Jamming to Collective Cell Migration Through a Boundary Induced Transition." *Soft Matter* 14: 3774–3782.

Cheung, K. J., V. Padmanaban, V. Silvestri, et al. 2016. "Polyclonal Breast Cancer Metastases Arise From Collective Dissemination of Keratin 14-Expressing Tumor Cell Clusters." *Proceedings of the National Academy of Sciences of the United States of America* 113: E854–E863.

Ciamarra, M. P., M. Nicodemi, and A. Coniglio. 2010. "Recent Results on the Jamming Phase Diagram." *Soft Matter* 6: 2871–2874.

Cox, T. R. 2021. "The Matrix in Cancer." *Nature Reviews Cancer* 21, no. 4: 217–238.

Curvello, R., V. Kast, P. Ordóñez-Morán, A. Mata, and D. Loessner. 2023. "Biomaterial-Based Platforms for Tumour Tissue Engineering." *Nature Reviews Materials* 8: 314–330.

Dagogo-Jack, I., and A. T. Shaw. 2017. "Tumour Heterogeneity and Resistance to Cancer Therapies." *Nature Reviews Clinical Oncology* 15: 81–94.

Das, P., H. A. Vinutha, and S. Sastry. 2020. "Unified Phase Diagram of Reversible–Irreversible, Jamming, and Yielding Transitions in Cyclically Sheared Soft-Sphere Packings." *Proceedings of the National Academy of Sciences of the United States of America* 117: 10203–10209.

Diz-Muñoz, A., D. A. Fletcher, and O. D. Weiner. 2013. "Use the Force: Membrane Tension as an Organizer of Cell Shape and Motility." *Trends in Cell Biology* 23: 47.

Dombroski, J. A., J. M. Hope, N. S. Sarna, and M. R. King. 2021. "Channeling the Force: Piezo1 Mechanotransduction in Cancer Metastasis." *Cells* 10: 2815.

Driscoll, M. K., and G. Danuser. 2015. "Quantifying Modes of 3D Cell Migration." *Trends in Cell Biology* 25: 749–759.

Eble, J. A., and S. Niland. 2019. "The Extracellular Matrix in Tumor Progression and Metastasis." *Clinical & Experimental Metastasis* 36: 171–198.

Egeblad, M., E. S. Nakasone, and Z. Werb. 2010. "Tumors as Organs: Complex Tissues That Interface With the Entire Organism." *Developmental Cell* 18: 884–901.

Elosegui-Artola, A., I. Andreu, A. E. M. Beedle, et al. 2017. "Force Triggers YAP Nuclear Entry by Regulating Transport Across Nuclear Pores." *Cell* 171: 1397–1410.

Fares, J., M. Y. Fares, H. H. Khachfe, H. A. Salhab, and Y. Fares. 2020. "Molecular Principles of Metastasis: A Hallmark of Cancer Revisited." *Signal Transduction and Targeted Therapy* 5, no. 1: 1–17.

Fisher, R., L. Pusztai, and C. Swanton. 2013. "Cancer Heterogeneity: Implications for Targeted Therapeutics." *British Journal of Cancer* 108: 479–485.

Foty, R. A., and M. S. Steinberg. 2005. "The Differential Adhesion Hypothesis: A Direct Evaluation." *Developmental Biology* 278: 255–263.

Franchi, M., K. Kyriakopoulou, and C. T. Mierke. 2024. "Extracellular Matrix Cues Regulate Mechanosensing and Mechanotransduction of Cancer Cells." *Cells* 13: 96.

Friedl, P., and D. Gilmour. 2009. "Collective Cell Migration in Morphogenesis, Regeneration and Cancer." *Nature Reviews Molecular Cell Biology* 10: 445–457. https://doi.org/10.1038/nrm2720.

Fuhs, T., F. Wetzel, A. W. Fritsch, et al. 2022. "Rigid Tumours Contain Soft Cancer Cells." *Nature Physics* 18, no. 12: 1510–1519.

Garcia, S., E. Hannezo, J. Elgeti, J. F. Joanny, P. Silberzan, and N. S. Gov. 2015. "Physics of Active Jamming During Collective Cellular Motion in a Monolayer." *Proceedings of the National Academy of Sciences of the United States of America* 112: 15314–15319.

Gensbittel, V., M. Kräter, S. Harlepp, I. Busnelli, J. Guck, and J. G. Goetz. 2021. "Mechanical Adaptability of Tumor Cells in Metastasis." *Developmental Cell* 56: 164–179.

George, S., J. A. J. Martin, V. Graziani, and V. Sanz-Moreno. 2023. "Amoeboid Migration in Health and Disease: Immune Responses Versus Cancer Dissemination." *Frontiers in Cell and Development Biology* 10: 1091801.

Gjorevski, N., A. S. Piotrowski, V. D. Varner, and C. M. Nelson. 2015. "Dynamic Tensile Forces Drive Collective Cell Migration Through Three-Dimensional Extracellular Matrices." *Scientific Reports* 5: 1–13.

Goossens, S., N. Vandamme, P. Van Vlierberghe, and G. Berx. 2017. "EMT Transcription Factors in Cancer Development Re-Evaluated: Beyond EMT and MET." *Biochimica et Biophysica Acta (BBA)–Reviews on Cancer* 1868: 584–591.

Grannemann, C., A. Pabst, A. Honert, et al. 2023. "Mechanical Activation of Lung Epithelial Cells Through the Ion Channel Piezo1 Activates the Metalloproteinases ADAM10 and ADAM17 and Promotes Growth Factor and Adhesion Molecule Release." *Biomaterials Advances* 152: 213516.

Graziani, V., I. Rodriguez-Hernandez, O. Maiques, and V. Sanz-Moreno. 2022. "The Amoeboid State as Part of the Epithelial-To-Mesenchymal Transition Programme." *Trends in Cell Biology* 32: 228–242.

Guan, J. L. 1997. "Role of Focal Adhesion Kinase in Integrin Signaling." *International Journal of Biochemistry & Cell Biology* 29: 1085–1096.

Gudipaty, S. A., J. Lindblom, P. D. Loftus, et al. 2017. "Mechanical Stretch Triggers Rapid Epithelial Cell Division Through Piezo1." *Nature* 543: 118–121.

Guimarães, C. F., L. Gasperini, A. P. Marques, and R. L. Reis. 2020. "The Stiffness of Living Tissues and Its Implications for Tissue Engineering." *Nature Reviews Materials* 5: 351–370.

Haeger, A., M. Krause, K. Wolf, and P. Friedl. 2014. "Cell Jamming: Collective Invasion of Mesenchymal Tumor Cells Imposed by Tissue Confinement." *Biochimica et Biophysica Acta (BBA) - General Subjects* 1840: 2386–2395.

Haerinck, J., S. Goossens, and G. Berx. 2023. "The Epithelial–Mesenchymal Plasticity Landscape: Principles of Design and Mechanisms of Regulation." *Nature Reviews Genetics* 24: 590–609.

Han, S. J., S. Kwon, and K. S. Kim. 2021. "Challenges of Applying Multicellular Tumor Spheroids in Preclinical Phase." *Cancer Cell International* 21: 1–19.

Heer, N. C., and A. C. Martin. 2017. "Tension, Contraction and Tissue Morphogenesis." *Development* 144: 4249–4260.

Henke, E., R. Nandigama, and S. Ergün. 2019. "Extracellular Matrix in the Tumor Microenvironment and Its Impact on Cancer Therapy." *Frontiers in Molecular Biosciences* 6: 160.

Heureaux-Torres, J., K. E. Luker, H. Haley, et al. 2018. "The Effect of Mechanosensitive Channel MscL Expression in Cancer Cells on 3D Confined Migration." *APL Bioengineering* 2: 032001.

Holt, J. R., W. Z. Zeng, E. L. Evans, et al. 2021. "Spatiotemporal Dynamics of PIEZO1 Localization Controls Keratinocyte Migration During Wound Healing." *eLife* 10: 1–24.

Huna, A., B. Nawrocki-Raby, T. Padilla-Benavides, et al. 2021. "Loss of the Metastasis Suppressor nme1, but Not of Its Highly Related Isoform nme2, Induces a Hybrid Epithelial–Mesenchymal State in Cancer Cells." *International Journal of Molecular Sciences* 22: 3718.

Ilina, O., P. G. Gritsenko, S. Syga, et al. 2020. "Cell–Cell Adhesion and 3D Matrix Confinement Determine Jamming Transitions in Breast Cancer Invasion." *Nature Cell Biology* 22: 1103–1115.

Jain, R. K., J. D. Martin, and T. Stylianopoulos. 2014. "The Role of Mechanical Forces in Tumor Growth and Therapy." *Annual Review of Biomedical Engineering* 16: 321–346.

Janmey, P. A., D. A. Fletcher, and C. A. Reinhart-King. 2020. "Stiffness Sensing by Cells." *Physiological Reviews* 100: 695–724.

Jo, J., S. Abdi Nansa, and D. H. Kim. 2020. "Molecular Regulators of Cellular Mechanoadaptation at Cell–Material Interfaces." *Frontiers in Bioengineering and Biotechnology* 8: 608569.

Kabla, A. J. 2012. "Collective Cell Migration: Leadership, Invasion and Segregation." *Journal of the Royal Society Interface* 9: 3268–3278.

Kalluri, R. 2016. "The Biology and Function of Fibroblasts in Cancer." *Nature Reviews Cancer* 16: 582–598.

Kang, W., J. Ferruzzi, C. P. Spatarelu, et al. 2021. "A Novel Jamming Phase Diagram Links Tumor Invasion to Non-equilibrium Phase Separation." *iScience* 24: 103252.

Khoo, A. S., T. M. Valentin, S. E. Leggett, et al. 2019. "Breast Cancer Cells Transition From Mesenchymal to Amoeboid Migration in Tunable Three-Dimensional Silk-Collagen Hydrogels." *ACS Biomaterials Science & Engineering* 5: 4341–4354.

Koushki, N., A. Ghagre, L. K. Srivastava, C. Molter, and A. J. Ehrlicher. 2023. "Nuclear Compression Regulates YAP Spatiotemporal Fluctuations in Living Cells." *Proceedings of the National Academy of Sciences of the United States of America* 120: e2301285120.

Krause, M., and K. Wolf. 2015. "Cancer Cell Migration in 3D Tissue: Negotiating Space by Proteolysis and Nuclear Deformability." *Cell Adhesion & Migration* 9: 357–366.

Kumari, A., S. M. Veena, R. Luha, and A. Tijore. 2023. "Mechanobiological Strategies to Augment Cancer Treatment." *ACS Omega* 8: 42072–42085.

Ladoux, B., and R. M. Mège. 2017. "Mechanobiology of Collective Cell Behaviours." *Nature Reviews Molecular Cell Biology* 18: 743–757.

Lämmermann, T., and M. Sixt. 2009. "Mechanical Modes of "Amoeboid" Cell Migration." *Current Opinion in Cell Biology* 21: 636–644.

Lawson-Keister, E., and M. L. Manning. 2021. "Jamming and Arrest of Cell Motion in Biological Tissues." *Current Opinion in Cell Biology* 72: 146–155.

Lee, H. P., F. Alisafaei, K. Adebawale, J. Chang, V. B. Shenoy, and O. Chaudhuri. 2021. "The Nuclear Piston Activates Mechanosensitive Ion Channels to Generate Cell Migration Paths in Confining Microenvironments." *Science Advances* 7: 1–13.

Lee, L. M., and A. P. Liu. 2015. "A Microfluidic Pipette Array for Mechanophenotyping of Cancer Cells and Mechanical Gating of Mechanosensitive Channels." *Lab on a Chip* 15: 264–273.

Lenne, P. F., and V. Trivedi. 2022. "Sculpting Tissues by Phase Transitions." *Nature Communications* 13: 1–14.

Li, C., S. Rezania, S. Kammerer, et al. 2015. "Piezo1 Forms Mechanosensitive Ion Channels in the Human MCF-7 Breast Cancer Cell Line." *Scientific Reports* 5: 1–9.

Li, M., X. Zhang, M. Wang, et al. 2022. "Activation of Piezo1 Contributes to Matrix Stiffness-Induced Angiogenesis in Hepatocellular Carcinoma." *Cancer Communications* 42: 1162–1184.

Ligorio, C., and A. Mata. 2023. "Synthetic Extracellular Matrices With Function-Encoding Peptides." *Nature Reviews Bioengineering* 1: 518–536.

Lintz, M., A. Muñoz, and C. A. Reinhart-King. 2017. "The Mechanics of Single Cell and Collective Migration of Tumor Cells." *Journal of Biomechanical Engineering* 139: 210051–210059.

Liu, A. J., and S. R. Nagel. 1998. "Jamming Is Not Just Cool any More." *Nature* 396: 21–22. https://doi.org/10.1038/23819.

Liu, A. P., O. Chaudhuri, and S. H. Parekh. 2017. "New Advances in Probing Cell-Extracellular Matrix Interactions." *Integrative Biology* 9: 383–405. https://doi.org/10.1039/c6ib00251j.

Liu, Q., Q. Luo, Y. Ju, and G. Song. 2020. "Role of the Mechanical Microenvironment in Cancer Development and Progression." *Cancer Biology & Medicine* 17: 282–292.

Lu, P., K. Takai, V. M. Weaver, and Z. Werb. 2011. "Extracellular Matrix Degradation and Remodeling in Development and Disease." *Cold Spring Harbor Perspectives in Biology* 3: 1–24.

Luo, M., G. Cai, K. K. Y. Ho, et al. 2022. "Compression Enhances Invasive Phenotype and Matrix Degradation of Breast Cancer Cells via Piezo1 Activation." *BMC Molecular and Cell Biology* 23: 1–17.

Malandrino, A., X. Trepat, R. D. Kamm, and M. Mak. 2019. "Dynamic Filopodial Forces Induce Accumulation, Damage, and Plastic Remodeling of 3D Extracellular Matrices." *PLoS Computational Biology* 15: e1006684.

Mason, D. E., J. M. Collins, J. H. Dawahare, et al. 2019. "YAP and TAZ Limit Cytoskeletal and Focal Adhesion Maturation to Enable Persistent Cell Motility." *Journal of Cell Biology* 218: 1369–1389.

Massagué, J., and A. C. Obenauf. 2016. "Metastatic Colonization by Circulating Tumour Cells." *Nature* 529: 298–306.

Mayor, R., and S. Etienne-Manneville. 2016. "The Front and Rear of Collective Cell Migration." *Nature Reviews Molecular Cell Biology* 17: 97–109.

Méhes, E., E. Mones, M. Varga, et al. 2023. "3D Cell Segregation Geometry and Dynamics Are Governed by Tissue Surface Tension Regulation." *Communications Biology* 6: 1–14.

Meng, Y., B. K. Primkulov, Z. Yang, C. Y. Kwok, and R. Juanes. 2020. "Jamming Transition and Emergence of Fracturing in Wet Granular Media." *Physical Review Research* 2: 022012.

Merino-Casallo, F., M. J. Gomez-Benito, S. Hervas-Raluy, and J. M. Garcia-Aznar. 2022. "Unravelling Cell Migration: Defining Movement From the Cell Surface." *Cell Adhesion & Migration* 16: 25–64.

Mierke, C. T. 2021. "Viscoelasticity Acts as a Marker for Tumor Extracellular Matrix Characteristics." *Frontiers in Cell and Development Biology* 9: 785138.

Mitchel, J. A., A. Das, M. J. O'Sullivan, et al. 2020. "In Primary Airway Epithelial Cells, the Unjamming Transition Is Distinct From the Epithelial-To-Mesenchymal Transition." *Nature Communications* 11: 1–14.

Murthy, S. E., A. E. Dubin, and A. Patapoutian. 2017. "Piezos Thrive Under Pressure: Mechanically Activated Ion Channels in Health and Disease." *Nature Reviews Molecular Cell Biology* 18: 771–783.

Nagle, I., A. Richert, M. Quinteros, et al. 2022. "Surface Tension of Model Tissues During Malignant Transformation and Epithelial–Mesenchymal Transition." *Frontiers in Cell and Development Biology* 10: 926322.

Nasrollahi, S., C. Walter, A. J. Loza, G. V. Schimizzi, G. D. Longmore, and A. Pathak. 2017. "Past Matrix Stiffness Primes Epithelial Cells and Regulates Their Future Collective Migration Through a Mechanical Memory." *Biomaterials* 146: 146–155.

Nematbakhsh, Y., K. T. Pang, and C. T. Lim. 2017. "Correlating the Viscoelasticity of Breast Cancer Cells With Their Malignancy." *Convergent Science Physical Oncology* 3: 034003.

Nguyen, L. T. S., M. A. C. Jacob, E. Parajón, and D. N. Robinson. 2022. "Cancer as a Biophysical Disease: Targeting the Mechanical-Adaptability Program." *Biophysical Journal* 121: 3573–3585.

Nia, H. T., L. L. Munn, and R. K. Jain. 1979. "Physical Traits of Cancer." *Science* 370: 2020.

Nieto, M. A., R. Y. Y. J. Huang, R. A. A. Jackson, and J. P. P. Thiery. 2016. "EMT: 2016." *Cell* 166: 21–45.

Oswald, L., S. Grosser, D. M. Smith, and J. A. Käs. 2017. "Jamming Transitions in Cancer." *Journal of Physics D: Applied Physics* 50: 483001.

Pajic-Lijakovic, I., R. Eftimie, M. Milivojevic, and S. P. A. Bordas. 2023. "Multi-Scale Nature of the Tissue Surface Tension: Theoretical Consideration on Tissue Model Systems." *Advances in Colloid and Interface Science* 315: 102902.

Pajic-Lijakovic, I., and M. Milivojevic. 2019. "Jamming State Transition and Collective Cell Migration." *Journal of Biological Engineering* 13: 1–12.

Palamidessi, A., C. Malinverno, E. Frittoli, et al. 2019. "Unjamming Overcomes Kinetic and Proliferation Arrest in Terminally Differentiated Cells and Promotes Collective Motility of Carcinoma." *Nature Materials* 18: 1252–1263.

Panciera, T., L. Azzolin, M. Cordenonsi, and S. Piccolo. 2017. "Mechanobiology of YAP and TAZ in Physiology and Disease." *Nature Reviews Molecular Cell Biology* 18: 758–770.

Paňková, K., D. Rösel, M. Novotný, and J. Brábek. 2010. "The Molecular Mechanisms of Transition Between Mesenchymal and Amoeboid Invasiveness in Tumor Cells." *Cellular and Molecular Life Sciences* 67: 63–71.

Park, J. A., L. Atia, J. A. Mitchel, J. J. Fredberg, and J. P. Butler. 2016. "Collective Migration and Cell Jamming in Asthma, Cancer and Development." *Journal of Cell Science* 129: 3375–3383.

Park, J. A., J. H. Kim, D. Bi, et al. 2015. "Unjamming and Cell Shape in the Asthmatic Airway Epithelium." *Nature Materials* 14: 1040–1048.

Pastushenko, I., and C. Blanpain. 2019. "EMT Transition States During Tumor Progression and Metastasis." *Trends in Cell Biology* 29: 212–226.

Paszek, M. J., N. Zahir, K. R. Johnson, et al. 2005. "Tensional Homeostasis and the Malignant Phenotype." *Cancer Cell* 8: 241–254.

Pawlizak, S., A. W. Fritsch, S. Grosser, et al. 2015. "Testing the Differential Adhesion Hypothesis Across the Epithelial–Mesenchymal Transition." *New Journal of Physics* 17: 083049.

Pawluchin, A., and M. Galic. 2022. "Moving Through a Changing World: Single Cell Migration in 2D vs. 3D." *Frontiers in Cell and Development Biology* 10: 1080995.

Petrie, R. J., N. Gavara, R. S. Chadwick, and K. M. Yamada. 2012. "Nonpolarized Signaling Reveals Two Distinct Modes of 3D Cell Migration." *Journal of Cell Biology* 197: 439–455.

Petrie, R. J., and K. M. Yamada. 2012. "At the Leading Edge of Three-Dimensional Cell Migration." *Journal of Cell Science* 125: 5917–5926.

Petrie, R. J., and K. M. Yamada. 2016. "Multiple Mechanisms of 3D Migration: The Origins of Plasticity." *Current Opinion in Cell Biology* 42: 7–12.

Pickup, M. W., J. K. Mouw, and V. M. Weaver. 2014. "The Extracellular Matrix Modulates the Hallmarks of Cancer." *EMBO Reports* 15: 1243–1253.

Plou, J., Y. Juste-Lanas, V. Olivares, et al. 2018. "From Individual to Collective 3D Cancer Dissemination: Roles of Collagen Concentration and TGF-β." *Scientific Reports* 8: 1–14.

Polacheck, W. J., I. K. Zervantonakis, and R. D. Kamm. 2013. "Tumor Cell Migration in Complex Microenvironments." *Cellular and Molecular Life Sciences* 70: 1335–1356.

Purkayastha, P., M. K. Jaiswal, and T. P. Lele. 2021. "Molecular Cancer Cell Responses to Solid Compressive Stress and Interstitial Fluid Pressure." *Cytoskeleton* 78: 312–322.

Qiao, Y., J. Chen, Y. B. Lim, et al. 2017. "Yap Regulates Actin Dynamics Through ARHGAP29 and Promotes Metastasis." *Cell Reports* 19: 1495–1502.

Raghuraman, S., A. S. Schubert, S. Bröker, et al. 2022. "Pressure Drives Rapid Burst-Like Coordinated Cellular Motion From 3D Cancer Aggregates." *Advanced Science* 9: 2104808.

Sadati, M., N. Taheri Qazvini, R. Krishnan, C. Y. Park, and J. J. Fredberg. 2013. "Collective Migration and Cell Jamming." *Differentiation* 86: 121–125.

Salvatore, V., G. Teti, S. Focaroli, M. C. Mazzotti, A. Mazzotti, and M. Falconi. 2017. "The Tumor Microenvironment Promotes Cancer Progression and Cell Migration." *Oncotarget* 8: 9608–9616.

Saraswathibhatla, A., D. Indana, and O. Chaudhuri. 2023. "Cell–Extracellular Matrix Mechanotransduction in 3D." *Nature Reviews Molecular Cell Biology* 24: 495–516.

Sauer, F., S. Grosser, M. Shahryari, et al. 2023. "Changes in Tissue Fluidity Predict Tumor Aggressiveness in Vivo." *Advanced Science* 10: 2303523.

Schultz, K. M., K. A. Kyburz, and K. S. Anseth. 2015. "Measuring Dynamic Cell-Material Interactions and Remodeling During 3D Human Mesenchymal Stem Cell Migration in Hydrogels." *Proceedings of the National Academy of Sciences of the United States of America* 112: E3757–E3764.

Schulz, M., A. Salamero-Boix, K. Niesel, T. Alekseeva, and L. Sevenich. 2019. "Microenvironmental Regulation of Tumor Progression and Therapeutic Response in Brain Metastasis." *Frontiers in Immunology* 10: 1713.

Shellard, A., and R. Mayor. 2020. "Rules of Collective Migration: From the Wildebeest to the Neural Crest." *Philosophical Transactions of the Royal Society B* 375: 20190387.

Sitarska, E., and A. Diz-Muñoz. 2020. "Pay Attention to Membrane Tension: Mechanobiology of the Cell Surface." *Current Opinion in Cell Biology* 66: 11–18.

Skamrahl, M., J. Schünemann, M. Mukenhirn, et al. 2023. "Cellular Segregation in Cocultures Is Driven by Differential Adhesion and Contractility on Distinct Timescales." *Proceedings of the National Academy of Sciences of the United States of America* 120: e2213186120.

Srivastava, N., D. Traynor, M. Piel, A. J. Kabla, and R. R. Kay. 2020. "Pressure Sensing Through Piezo Channels Controls Whether Cells Migrate With Blebs or Pseudopods." *Proceedings of the National Academy of Sciences of the United States of America* 117: 2506–2512.

Steeg, P. S. 2016. "Targeting metastasis." *Nature reviews cancer* 16, no. 4: 201–218.

Steinberg, M. S. 2007. "Differential Adhesion in Morphogenesis: A Modern View." *Current Opinion in Genetics & Development* 17: 281–286.

Tabassum, D. P., and K. Polyak. 2015. "Tumorigenesis: it takes a village." *Nature Reviews Cancer* 15: 473–483.

Takai, K., A. le, V. M. Weaver, and Z. Werb. 2016. "Targeting the Cancer-Associated Fibroblasts as a Treatment in Triple-Negative Breast Cancer." *Oncotarget* 7: 82889–82901.

Tan, X., J. Heureaux, and A. P. Liu. 2015. "Cell Spreading Area Regulates Clathrin-Coated Pit Dynamics on Micropatterned Substrate." *Integrative Biology* 7: 1033–1043.

Trappe, V., V. Prasad, L. Cipelletti, P. N. Segre, and D. A. Weitz. 2001. "Jamming Phase Diagram for Attractive Particles." *Nature* 411: 772–775.

Trepat, X., and E. Sahai. 2018. "Mesoscale Physical Principles of Collective Cell Organization." *Nature Physics* 14, no. 7: 671–682.

Trepat, X., M. Wasserman, T. Angelini, et al. 2009. "Physical Forces During Collective Cell Migration." *Nature Physics* 5: 426–430.

Tsai, T. Y. C., R. M. Garner, and S. G. Megason. 2022. "Adhesion-Based Self-Organization in Tissue Patterning." *Annual Review of Cell and Developmental Biology* 38: 349–374. https://doi.org/10.1146/annurev-cellbio-120420-100215.

Tse, J. M., G. Cheng, J. A. Tyrrell, et al. 2012. "Mechanical Compression Drives Cancer Cells Toward Invasive Phenotype." *Proceedings of the National Academy of Sciences* 109: 911–916.

Van Der Net, A., Z. Rahman, A. Bordoloi, et al. 2024. "EMT-Dependent Cell-Matrix Interactions Are Linked to Unjamming Transitions in Cancer Spheroid Invasion." *bioRxiv*. https://doi.org/10.1101/2024.05.08.593120.

Van Helvert, S., C. Storm, and P. Friedl. 2017. "Mechanoreciprocity in Cell Migration." *Nature Cell Biology* 20, no. 1: 8–20.

Varadarajan, S., S. A. Chumki, R. E. Stephenson, et al. 2022. "Mechanosensitive Calcium Flashes Promote Sustained RhoA Activation During Tight Junction Remodeling." *Journal of Cell Biology* 221: 1–21.

Vesperini, D., G. Montalvo, B. Qu, and F. Lautenschläger. 2021. "Characterization of Immune Cell Migration Using Microfabrication." *Biophysical Reviews* 13: 185–202.

Wang, J., J. Jiang, X. Yang, G. Zhou, L. Wang, and B. Xiao. 2022. "Tethering Piezo Channels to the Actin Cytoskeleton for Mechanogating via the Cadherin-β-Catenin Mechanotransduction Complex." *Cell Reports* 38: 110342.

Wang, Y., K. F. Goliwas, P. E. Severino, et al. 2020. "Mechanical Strain Induces Phenotypic Changes in Breast Cancer Cells and Promotes Immunosuppression in the Tumor Microenvironment." *Laboratory Investigation* 100: 1503–1516.

Welch, D. R., and D. R. Hurst. 2019. "Defining the Hallmarks of Metastasis." *Cancer Research* 79: 3011–3027.

Willy, N. M., J. P. Ferguson, S. D. Huber, et al. 2017. "Membrane Mechanics Govern Spatiotemporal Heterogeneity of Endocytic Clathrin Coat Dynamics." *Molecular Biology of the Cell* 28: 3480–3488.

Winkler, J., A. Abisoye-Ogunniyan, K. J. Metcalf, and Z. Werb. 2020. "Concepts of Extracellular Matrix Remodelling in Tumour Progression and Metastasis." *Nature Communications* 11: 1–19.

Wirtz, D., K. Konstantopoulos, and P. C. Searson. 2011. "The Physics of Cancer: The Role of Physical Interactions and Mechanical Forces in Metastasis." *Nature Reviews Cancer* 11: 512–522.

Wu, D., K. M. Yamada, and S. Wang. 2023. "Tissue Morphogenesis Through Dynamic Cell and Matrix Interactions." *Annual Review of Cell and Developmental Biology* 39: 123–144. https://doi.org/10.1146/annurev-cellbio-020223-031019.

Wu, P. H., D. M. Gilkes, and D. Wirtz. 2016. "The Biophysics of 3D Cell." *Migration* 47: 549–567. https://doi.org/10.1146/annurev-biophys-070816-033854.

Wu, J-S., J. Jiang, B-J. Chen, et al. 2021. "Plasticity of Cancer Cell Invasion: Patterns and Mechanisms." *Translational Oncology* 14: 100899.

Wu, X. S., S. Elias, H. Liu, et al. 2017. "Membrane Tension Inhibits Rapid and Slow Endocytosis in Secretory Cells." *Biophysical Journal* 113: 2406–2414.

Xie, Y., M. Wang, M. Cheng, Z. Gao, and G. Wang. 2019. "The Viscoelastic Behaviors of Several Kinds of Cancer Cells and Normal Cells." *Journal of the Mechanical Behavior of Biomedical Materials* 91: 54–58.

Xu, J., S. L. Murphy, K. D. Kochanek, and E. Arias. 2021. Mortality in the United States, 2021 Key Findings Data From the National Vital Statistics System.

Xu, R., P. Yin, J. Wei, and Q. Ding. 2023. "The Role of Matrix Stiffness in Breast Cancer Progression: A Review." *Frontiers in Oncology* 13: 1284926.

Yamada, K. M., and M. Sixt. 2019. "Mechanisms of 3D Cell Migration." *Nature Reviews Molecular Cell Biology* 20: 738–752.

Yamaguchi, H., J. Wyckoff, and J. Condeelis. 2005. "Cell Migration in Tumors." *Current Opinion in Cell Biology* 17: 559–564.

Yamamoto, A., A. E. Doak, and K. J. Cheung. 2023. "Orchestration of Collective Migration and Metastasis by Tumor Cell Clusters." *Annual*

Review of Pathology: Mechanisms of Disease 18: 231–256. https://doi.org/10.1146/annurev-pathmechdis-031521-023557.

Yan, H., D. Ramirez-Guerrero, J. Lowengrub, and M. Wu. 2021. "Stress Generation, Relaxation and Size Control in Confined Tumor Growth." *PLoS Computational Biology* 17: e1009701.

Yang, D., J. Liu, H. Qian, and Q. Zhuang. 2023. "Cancer-Associated Fibroblasts: From Basic Science to Anticancer Therapy." *Experimental & Molecular Medicine* 55: 1322–1332.

Yang, J., P. Antin, G. Berx, et al. 2020. "Guidelines and Definitions for Research on Epithelial–Mesenchymal Transition." *Nature Reviews Molecular Cell Biology* 21: 341–352.

Yang, X., D. Bi, M. Czajkowski, M. Merkel, M. L. Manning, and M. C. Marchetti. 2017. "Correlating Cell Shape and Cellular Stress in Motile Confluent Tissues." *Proceedings of the National Academy of Sciences of the United States of America* 114: 12663–12668.

Yang, Y., H. Zheng, Y. Zhan, and S. Fan. 2019. "An Emerging Tumor Invasion Mechanism About the Collective Cell Migration." *American Journal of Translational Research* 11: 5301–5312.

Yoshida, G. J. 2020. "Regulation of Heterogeneous Cancer-Associated Fibroblasts: The Molecular Pathology of Activated Signaling Pathways." *Journal of Experimental & Clinical Cancer Research* 39: 1–15.

Yu, Y., X. Wu, S. Liu, et al. 2020. "Piezo1 Regulates Migration and Invasion of Breast Cancer Cells via Modulating Cell Mechanobiological Properties." *Acta Biochimica et Biophysica Sinica* 53: 10–18.

Zanconato, F., M. Cordenonsi, and S. Piccolo. 2019. "YAP and TAZ: A Signalling Hub of the Tumour Microenvironment." *Nature Reviews Cancer* 19, no. 8: 454–464.

Zhang, J., T. S. Majmudar, M. Sperl, and R. P. Behringer. 2010. "Jamming for a 2D Granular Material." *Soft Matter* 6: 2982–2991.

Zheng, Y., and D. Pan. 2019. "The Hippo Signaling Pathway in Development and Disease." *Developmental Cell* 50: 264–282.

Zhou, H., M. Wang, Y. Zhang, et al. 2022. "Functions and Clinical Significance of Mechanical Tumor Microenvironment: Cancer Cell Sensing, Mechanobiology and Metastasis." *Cancer Communications* 42: 374–400.