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Subcellular regulation of cancer cell mechanics

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Cancer cells exhibit altered biophysical and biomechanical properties that contribute to an overall altered mechanical phenotype. Increasing evidence demonstrates that cancer cells are often associated with decreased bulk stiffness and higher contractility, properties that facilitate increased motility and invasiveness. These changes in cellular properties are most often due to subcellular alterations in the cytoskeletal organization that results from both changes in intracellular regulators as well as changes to the tumor microenvironment. This review will highlight recent key findings describing the role of upregulated cytoskeletal scaffolding proteins and signaling circuits, as well as microenvironmental cues that influence cytoskeletal regulation and epithelial-to-mesenchymal transition to alter cancer cell stiffness and contractility. We also briefly discuss the emerging role of extracellular microvesicles in long-range cell–cell modulation of cytoskeletal mechanics and malignant transformation.

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Introduction

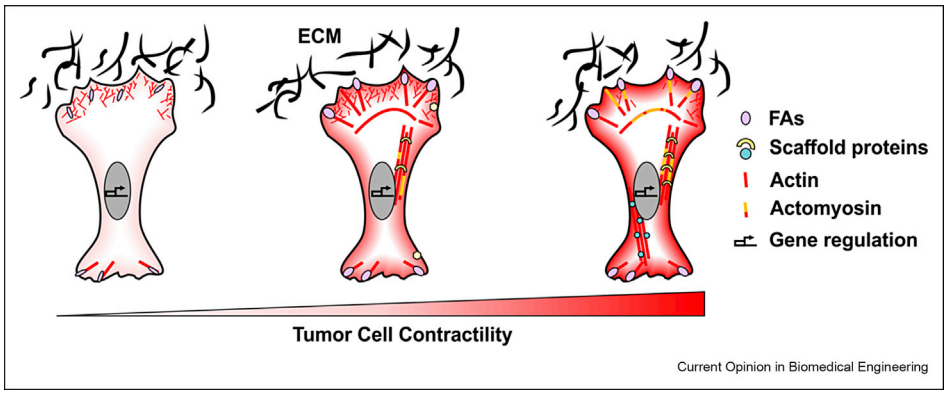
During metastasis, cancer cells undergo a multi-step process, where they break free from the primary tumor site, migrate through the stroma, and enter either the vascular or lymphatic systems to disseminate into secondary sites [1]. Interestingly, cancer cells display drastically different mechanical properties when compared to their non-tumorigenic counterparts [1–4]. In addition, cancer cells as well as tumor-initiating and tumor-repopulating cells clearly do not adapt to mechanical cues in the same ways as non-tumorigenic cells [5–8]. Recently, researchers have identified that the altered and changing mechanical phenotype of cancer cells is a significant aspect of the metastatic process. Cells sense, process, and react to mechanical and biophysical cues from their environment using an interconnected system of mechanosensors that are critical to their ability to alter motility to navigate the tumor stroma [6]. Cancer cells adaptively alter their motility through modifications to actin polymerization, cell adhesions, and actomyosin contractility in response to the surrounding microenvironment [1,9]. Thus, an emergent area of research seeks to understand the subcellular components that contribute to the altered mechanics observed in cancer cells.

Despite the fact that tumor tissue is stiffer than healthy tissue [2,6], individual cancer cells are frequently more compliant when compared to healthy cells [3,4]. In a number of cancer types, cancer cells demonstrate a lower bulk stiffness compared to non-tumorigenic cells [3,4]. Furthermore, invasive cancer cell lines demonstrate lower bulk stiffness compared to non-invasive cell lines [10]. However, cancer cells have also been associated with high contractility, where cancer cell contractility is proportional to metastatic potential [5]. In this review, we will discuss the characteristic cellular mechanics properties identified in cancer cells, as well as the alterations in cytoskeletal organization and regulation that contribute to these changes in cellular mechanics.

Cytoskeletal regulation and organization in cancer cells

The cytoskeleton serves as a scaffold for signaling, a mechanical coupler to the extracellular environment, and a mechanosensor [9]. Metastatic cancer cells use the cytoskeleton to strengthen protrusions that allow them to escape from the primary tumor site and invade through surrounding tissue [9]. Actin polymerization drives the plasma membrane forward and actomyosin contractility pulls the plasma membrane to produce hydrostatic pressure, controlling cell morphology [9]. Dynamic spatial and temporal regulation and reorganization of the cytoskeleton is fundamental to such events [11]. As such, tumorigenesis has been correlated with modulation of cytoskeletal organization, cytoskeletal proteins, and focal adhesion (FA) turnover (Figure 1). Indeed, there is an increasing interest in tumor-specific scaffolding and signaling molecules that

Figure 1



Schematic representation of tumor cell in three different mechanical states. In all cases, the cell cytoskeleton is mechanically coupled to the ECM through FAs, and several actin scaffolding proteins can further alter cell mechanics through their effects on overall actin organization and control of actomyosin contractility. Furthermore, cellular response to ECM stiffness depends on the innate contractility state of the cell, but conversely, ECM stiffness can alter cellular mechanical state by influencing gene expression.

act as regulators of the cytoskeleton and cellular mechanics in cancer.

Actin filaments

Contractile actin bundles that connect the cytoskeleton to the extracellular matrix (ECM) at FA sites, known as stress fibers, are especially prominent in cancer cells [9]. The formation and alignment of contractile stress fibers, which is essential for cell migration, is a mechanosensitive process dependent upon actin filament assembly and disassembly [12]. Many actin-bundling proteins have elevated expression in various metastatic tumors and have been correlated with tumor progression and increased aggressiveness [13–18]. More recent work has shown that the actin-bundling proteins palladin, tropomyosin, and fascin directly modulate cancer cell mechanics. Palladin, a dynamic actin-bundling protein that binds actin to actin-associated proteins, is important for FA maturation, radial stress fiber formation, and modulating traction forces and mechanosensing [16,19]. In tumor associated fibroblasts, palladin-knockout cells exert higher traction forces, demonstrate higher sensitivity to matrix stiffness changes, and have an intrinsically different capacity for force generation compared to control cells [19]. Further, downregulation of palladin via miRNAs suppressed metastasis in a breast cancer mouse model [20]. Expression of the actin-bundling protein tropomyosin correlates with stress fiber formation [13] and impacts cell stiffness through intracellular tension generated via myosin II activity [21]. Fascin crosslinks filaments into parallel bundles at stress fiber termini, preventing myosin II association with actin, and reducing tension force generation and contractility [22,23]. Conversely, fascin-depleted cells form thick stress fibers associated with many myosin II molecules, and they exert high traction forces [23]. Blocking the actin-bundling capacity of fascin effectively blocks cell migration and invasion *in vitro*, and metastasis *in vivo*. Other actin-bundling proteins, namely α-Actinin-4 (ACTN4) and zyxin, are involved in tumorigenesis; however, further work is needed to identify their specific contribution to cancer cell mechanics. ACTN4 is involved in regulating actin filament flexibility at the leading edge of cancer cells, and is frequently amplified and overexpressed in cancers [17,24,25]. In other non-cancerous cell types, ACTN4 has been shown to regulate cell force generation [26]. Similarly, LIM domain protein zyxin regulates actin dynamics in response to mechanical forces and its expression correlates with cancer cell lines with higher malignancy [18].

Scaffolding proteins also directly regulate actin dynamics and organization at the cell membrane. The Ezrin-Radixin-Moesin (ERM) family are the most well-known proteins that crosslink actin filaments with the plasma membrane [27]; however, others have been identified. The cytoskeletal scaffolding protein, Moesin-Ezerin-Radixin-Like Protein (merlin) links actin filaments to the cell membrane or membrane glycoproteins, and is a tumor suppressor [27]. Recently, merlin has been identified as a crucial mechanotransducer and contributor in driving collective cell migration [28]. Triggered by the intracellular pulling force of the leading cell during collective migration and actomyosin-based cell contractility, merlin localizes from the cortical cell–cell junction in stationary cells to the cytoplasm in migratory cells. At this position, merlin coordinates polarized Rac activation and lamellipodium formation. As Rac1 is activated at the front position and RhoA is activated at the end position of migrating cells, regulation through merlin leads to phenotypic plasticity of cancer cell migration [28]. Similarly, three Striatin-interacting Phosphatase and Kinase (STRIPAK) complex components, FAM40A, FAM40B, and STRN3, have