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Mini Review

Mechanical and Systems Biology of Cancer

Fabian Spill [a,1], Chris Bakal [b], Michael Mak [c,*]

[a] School of Mathematics, University of Birmingham, Birmingham B15 2TT, UK
[b] Division of Cancer Biology, The Institute of Cancer Research, London SW3 6JB, UK
[c] Department of Biomedical Engineering, Yale University, New Haven, USA

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ABSTRACT

Mechanics and biochemical signaling are both often deregulated in cancer, leading to cancer cell phenotypes that exhibit increased invasiveness, proliferation, and survival. The dynamics and interactions of cytoskeletal components control basic mechanical properties, such as cell tension, stiffness, and engagement with the extracellular environment, which can lead to extracellular matrix remodeling. Intracellular mechanics can alter signaling and transcription factors, impacting cell decision making. Additionally, signaling from soluble and mechanical factors in the extracellular environment, such as substrate stiffness and ligand density, can modulate cytoskeletal dynamics. Computational models closely integrated with experimental support, incorporating cancer-specific parameters, can provide quantitative assessments and serve as predictive tools toward dissecting the feedback between signaling and mechanics and across multiple scales and domains in tumor progression.

Contents

1. Introduction

The mechanical microenvironment in cancer is vastly altered compared to healthy tissue. Typically, the extracellular matrix (ECM) is stiffened in the tumor microenvironment [1–3], but individual cancer cells may actually be softer [4]. There is a bimodal distribution of nano-mechanical stiffness across advanced cancer tissues [5]. Moreover, more complex mechanical and geometric characteristics, including the fibrous matrix structure, porosity, or viscoelastic parameters may be changed in tumors [6, 7]. Similarly, solid and fluid stresses are greatly altered in cancers [8]. It is well known that cancers exhibit increased fluid pressures, in part due to remodeling of the vasculature and lymphatics [9].

The altered ECM stiffness and geometry of the tumor microenvironment are sensed by tumor cells via mechanosensing structures, which can activate intracellular signaling pathways that drive behaviors such as unrestrained proliferation, increased survival, tissue invasion, stemness, and drug resistance [10–12]. While cancer has been traditionally considered a genetic disease, alterations in ECM stiffness and geometry can force normal cells to adopt phenotypes characteristic of transformed and/or metastatic cells in the absence of any genetic

* Corresponding author at: School of Mathematics, University of Birmingham, Birmingham B15 2TT, UK.
E-mail address: Michael.Mak@Yale.edu (M. Mak).
[1] Equal contribution.

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change [13, 14]. Theoretical work suggests that environmental cues, coupled with various possible oncogenic alterations (e.g. overexpression of c-Src [15]), can drive cancer progression [16, 17]. Cancer progression can be promoted by genetic changes that alter how cells respond to ECM stiffness and geometry and that enable cancer cells to remodel their environment in ways that promote disease.

To open new therapeutic avenues that seek to manipulate the response of cancer cells to their environment as a way to treat cancer, predictive mathematical models are required to describe how cell fate decisions are due to interactions between tumor cells and their ECM and how these interactions differ between normal and cancer cells. The problem is inherently multiscale in nature and involves diverse components such as biochemical reactions, cell-matrix and cell-cell interactions, and tissue-level alterations. The field of mechanotransduction has long embraced modelling tools in order to describe how cells respond to mechanical and geometric cues, and these models serve as key starting points for more complex descriptions of how cancer cells interact with their ECM. For example, models have been developed that provide insights into diverse aspects of mechanobiology including: force-dependent molecular bonds [18–21], spatiotemporal organization of intracellular molecules [22–24], impact of cell shape [25–29], and the dynamics of the cytoskeleton [30–32]. Here we review some of these models and supporting experimental findings with a look toward the future. We first review recent work on cytoskeletal interactions that modulate intracellular mechanics and the propagation of cytoskeletal forces inside and outside the cell. Next we focus on the cell-matrix adhesion complexes that act as key signal transducers and mechanosensors. Finally, we review key signaling networks implicated in mechanotransduction.

1.1. Generation and Propagation of Intracellular Forces

The active actin cytoskeleton provides basic structure and force generation capabilities. The key components include actin filaments, actin crosslinking proteins (ACPs) such as alpha-actinin and filamin, and myosin II motors that generate contractility. Inside the cell, a large network of these components undergoes dynamic and stochastic interactions, spontaneously resulting in pattern formation – including the actin cortex at the cell periphery, thick contractile bundles of actin (stress fibers), and cell polarity (leading and trailing edges). Local interactions and kinetics can control overall, global functionality of the cytoskeletal network. In particular, actin turnover rates can modulate cytoskeletal network tension, and the interplay between actin turnover, actin crosslinking, and myosin II walking activity can regulate the morphological state of the network, from homogeneous morphologies to local clusters (Fig. 1a) [30]. Computational simulations can isolate individual features and determine their roles in cytoskeletal network behavior. For example, altering actin nucleation rates can modulate the stress fluctuation magnitudes in the cytoskeleton, a phenotype observed in intracellular microrheology experiments that modulate epidermal growth factor (EGF) signaling (known to influence actin nucleation) in breast cancer cells [33]. Additionally, spatial and temporal profiles are important in regulating cell behavior. These can be precisely tuned in computational models. For example, cell geometry and dimensionality influence the anisotropy and amplitude of intracellular stress fluctuations [34]. While overall cell tensions have an intuitive role of enabling cells to apply forces onto their substrate (e.g. the ECM) and migrate, intracellular stress fluctuations can facilitate the redistribution of organelles and molecular components inside the crowded cytoplasmic space [35]. Furthermore, malignant tumor cells appear to exhibit larger intracellular displacement and stress fluctuations compared to benign counterparts, as shown by experiments measuring intracellular stiffness and force fluctuations [35]. Cytoskeletal mechanics and fluctuations are the result of the interactions between many cytoskeletal components, each undergoing dynamic processes (turnover, walking, binding, unbinding, etc.). Computational network models of the cytoskeleton, based on physical principles (reaction kinetics, mechanics) and incorporating realistic, experimentally tangible features, can help dissect the local, molecular-level contributions to experimentally observable mechanical cellular phenotypes. High resolution experimental techniques, e.g. super resolution imaging or atomic force microscopy, can help guide the development and validation of models of fine and distinct cytoskeletal features [36]. Furthermore, models coupling cytoskeletal forces to critical intracellular and extracellular features, particularly the nucleus and the ECM, can start to elucidate a more holistic picture of cell behavior.

Cytoskeletal forces can be transmitted to the cell nucleus via the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex [37]. Substrate stiffness modulates cytoskeletal tension and thus nuclear stress and shape, which interestingly also modulates the expression levels of a key nucleoskeletal protein lamin A, nuclear stiffness, and stem cell differentiation [38]. The mechanical properties of the nucleus can also influence nuclear shape and dynamics during cell deformation and invasion through confined spaces (e.g. ECM pores or endothelial junctions). Large nuclear deformations can lead to rupture and DNA damage, as observed in experimental studies of cancer cells invading through highly confined constrictions [39, 40]. Computational models coupling cellular forces to the nucleus can generate quantitative details of nuclear deformation and mechanical remodeling during physiological processes and draw insights toward differences in nuclear behavior due to biochemical or structural alterations. For example, experiments show that lamin A/C deficiency leads to more plastic remodeling of the nucleus after larger strains, which can be captured in a continuum model of the nucleus featuring a hyperelastic shell and a poroelastoplastic core (Fig. 1b) [41]. Furthermore, the role of different types of lamins (A and B) in regulating nuclear shape and geometry can be explored in continuum models through incorporating heterogeneous material profiles. In particular, a preferred mesh size difference between lamin A and lamin B appears to explain nuclear blebbing tendencies [42].

In many types of solid tumors, cancer cells are embedded in a dense fibrillar matrix. Cytoskeletal forces are transmitted into the ECM via cell-matrix adhesions, which can lead to ECM remodeling and propagate mechanical signals to surrounding cells [43]. Stiffer substrates tend to promote increased cell traction forces and lead to a more invasive phenotype [44, 45]. Relaxation of tension in the substrate in laser ablation experiments [46, 47] tends to revert cell invasiveness. Moreover, ECM networks exhibit nonlinear strain stiffening [48], suggesting potential mechanical feedback mechanisms. These phenomena have been demonstrated through a number of experimental studies. Complementarily, computational models can provide quantitative, mechanistic insights toward underlying driving factors of invasive behavior in 3D ECMs – particularly to a level of detail that may be unfeasible for experiments to achieve or parse out. Computationally intensive models can capture a high degree of local details observed in high resolution experiments of cell-ECM interactions. In a recent study, a model capturing an entire cell with dynamic protrusions inside a surrounding ECM showed that dynamic filopodia can act as rigidity sensors that facilitate durotaxis in HUVECs (Fig. 2a) [49]. While stiffness sensing (and many other cell behaviors) is a phenomenon exhibited by normal and cancer cells, cancer-related parameters can be tuned in generalizable models to explore disease phenotypes. In particular, the above model showed that the number and length of filopodia can modulate invasive behavior, supporting prior studies that showed that deregulation in filopodia-related functions and pathways are implicated in cancer progression and metastasis [50]. In another model that incorporates dynamic local forces and force-sensitive ECM fiber-fiber crosslinks, it is demonstrated that the coupling of mechanical forces and fiber-fiber biochemical kinetics can result in ECM densification near the cell boundary, consistent with experiments in tumor and

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