Regulation of Tumorigenesis and Development Mechanisms by Mechanical Properties of the Tumor Microenvironment

Bucheng Sun *

School of Mechanical Engineering, Wuhan Polytechnic University, JinYin Lake Campus, 36 Huanhu Middle Road, Dongxihu District, Wuhan, Hubei 430048, China

* Corresponding Author Email: 18271961269@163.com

Abstract. The mechanical properties of the tumor microenvironment play a pivotal role in tumorigenesis and progression. Tumor cells significantly reduce their own stiffness through cytoskeletal remodeling, while the extracellular matrix (ECM) stiffens and increases in viscosity. This bidirectional imbalance, characterized by cell softening and matrix stiffening, reshapes the tumor's biomechanical environment. This paper elucidates the alterations in mechanical properties within the tumor microenvironment and their biological impacts. These changes, through positive feedback, continuously exacerbate tumor proliferation and invasion. For instance, mechanical signals are converted into biochemical signals through mechanisms involving integrins and mechanosensitive ion channels, thereby driving cellular proliferation and immune evasion. Meanwhile, the stiffened ECM forms a physical barrier that hinders drug delivery. Additionally, this paper introduces a mechanical characterization tool, microfluidic chip technology, which simulates microvascular environments and provides potential strategies for tumor intervention and personalized therapy, such as mechanical model construction and personalized drug screening. In the future, intervening in ECM remodeling or Mechan transduction pathways is expected to overcome tumor drug resistance and enhance the efficacy of immunotherapy.

Keywords: Tumor development, microenvironment, mechanical signals.

1. Introduction

Tumor progression is partly a result of evolving cross-talk between different cell types within the tumor and its surrounding supportive tissue or tumor stroma. Essentially, it results from the synergistic effect of multiple factors, including gene mutations, epigenetic re-editing, abnormal activation of cellular signaling pathways, and dynamic remodeling of the tumor microenvironment. Traditional treatment methods (radiotherapy, chemotherapy, and targeted therapy) primarily target visible tumor cells, but their efficacy is often limited by drug resistance, physical barriers, and severe side effects. More critically, after eliminating cancer cells, such therapies often confront the tough issue of high tumor recurrence rates. The underlying reason is that they do not match the biological characteristics and mechanisms of action of tumor-promoting microenvironments and cancer stem cells, which actually play a decisive role. Over recent decades, the impact of mechanical factors on cancer has gradually gained attention as a peripheral perspective, serving as a critical supplement to traditional biological perspectives and providing novel targets and strategies for tumor treatment. It may break through the limitations of conventional therapies and achieve more comprehensive interventions through multi-dimensional physical factors. Analyzing the mechanisms of tumor development from the perspective of mechanical properties, and profoundly delving into alterations in mechanical properties of the tumor microenvironment and the mechanisms by which cells perceive and respond to biomechanical signals not only helps us better understand the essence of vital activities but also provides alternative perspectives and potential targets for tumor treatment strategies.

2. Mechanical Properties and Biological Basis of the Tumor Microenviroment

2.1. Cellular and ECM Mechanical Properties

The mechanical structure of cells is primarily supported by the cytoskeleton (comprised of microfilaments, microtubules, intermediate filaments), which in combination with the elastic cell membrane, jointly responds to and transmits mechanical stimulation signals, determining the mechanical characteristics of cells. The invasive cancer cells significantly enhance deformability and reduce stiffness through the actin cytoskeleton. The ECM is composed of proteins, such as collagen, fibronectin and polysaccharides which provides physical support and mediates the transmission of mechanical signals. It mainly consists of two major parts: the interstitial matrix and the basement membrane. The proportion of its components varies among different tissues. The Cancer-Associated Fibroblasts (CAFs) synthesize and deposit multiple ECM components such as collagen and fibronectin which leads to excessive ECM deposition, an increase in density and with the inversion of the type I to type III collagen ratio. Additionally, the CAFs secrete lysyl oxidase (LOX) to catalyze excessive cross-linking of collagen, resulting in a disordered arrangement, and the accumulation of glycosaminoglycans (GAGs) further leads to matrix hardening. The elevated enzymatic activity of these cross-linking enzymes strengthens collagen/elastin networks through covalent bonding, thereby impeding scar tissue resolution and elevating extracellular matrix rigidity [1]. Furthermore, ECM fibers have specific orientations and arrangements in normal tissue. Through contractile forces, CAFs straighten and align collagen fibers, resulting in a disordered fiber arrangement with a unidirectional linear alignment. This forms a dense barrier, further tightening the ECM and leading to an increase in the ECM's viscosity coefficient.

2.2. Mechanical Forces in the Tumor Microenviroment

During the malignant proliferation of solid tumors, components of the ECM and CAFs proliferate and gradually accumulate, accompanied by an increase in tumor size and hardness. This leads to local space restriction, thereby generating solid stresses from 1-10 kPa. The solid stress compresses adjacent vessels, induces luminal collapse and exacerbates local hypoxia. Notably, the central region of tumors exhibits the highest level of solid stress. Under the high-stress microenvironment, vascular permeability is markedly enhanced, driving tumor cells to migrate along the stress gradient, while numerous plasma proteins and fluids leak into the interstitium. Under the circumstance, dense ECM fibrosis obstructs fluid flow, increasing resistance to fluid flow and impeding the drainage of interstitial fluid. The interstitial fluid pressure (IFP) aggravates the local pressure, forming a therapeutic barrier that impedes the penetration of antibody-based drugs and influences cancer cells and stromal cells behavior. Tumor blood vessels exhibit a high degree of heterogeneity, featuring numerous tortuosities and branches. The morpho functional state of the cardiovascular system mechanically determines the blood flow and the mechanical constraints it exerts on this system, and the blood flow, through the mechanical sensing pathways stimulated by these constraints, modifies this morpho functional state [2]. In the case where the two form a causal loop, the uneven distribution of fluid shear stress (FSS) leads to disorganized tumor vascular branching.

3. Mechanical Signal Regulation on Tumor Progression in Tissues

3.1. Perception of Mechanical Signals and Conversion into Biochemical Signals

The integrin family serves as a critical bridge between the ECM and cytoskeleton. Their extracellular domains selectively bind to ECM components such as collagen and laminin, while intracellular domains recruit signaling adaptors like FAK to form mechanochemical signaling hubs [3]. Take integrin β1 as an example: this heterodimer activates the RhoA/ROCK pathway through the β1 subunit's intracellular kinase-binding domain, promoting pseudopod formation and ECM remodeling in hepatocellular carcinoma (HCC) cells [4]. Its expression level correlates significantly

with tumor invasive potential. Mechanosensitive ion channels like the Piezo1/2 family utilize trimeric propeller structures to detect membrane tension gradients. Transient pore dilation exceeding 3 nm mediates Ca^{2+}/Na^{+} ion fluxes, triggering calmodulin kinase II (CaMKII)-dependent signaling cascades. Studies reveal force-dependent polar distribution of Piezo1 channels on HCC cell membranes. Their activation induces nuclear translocation of YAP/TAZ transcriptional coactivators, remodeling cell migration polarity [5]. The cytoskeletal network performs dual functions in mechanical signaling and structural support. Microtubule systems use dynein-mediated nucleocytoplasmic transport to transmit contractile forces from adhesion stress fibers to lamin A/C, altering nuclear membrane permeability and chromatin compaction states. Intermediate filaments such as vimentin dynamically regulate nuclear matrix attachment regions (NMA) anchoring strength through stress-induced phosphorylation cascades, controlling chromatin accessibility of proliferation-related genes like c-Myc. Cyclic contractions of adhesion stress fibers activate Rho-associated coiled-coil forming protein kinase (ROCK) through FAK/Src phosphorylation, driving myosin II contractile ring formation and establishing cytoskeletal mechanical memory effects [6].

3.2. Mechanical Signal local Response in Tumor Development and Progression

3.2.1. Cell mechanical properties and morphological changes

The main characteristics of cellular carcinogenesis are the decrease in cell stiffness and the increase in ECM stiffness. These are the most obvious contradictions of static mechanical structure. This "soft-hard" bidirectional remodeling profoundly affects the biological behavior of tumor cells. On the one hand, cells dynamically regulate the physical properties of ECM through active contractile force and mechanical remodeling ability. On the other hand, the ECM triggers the assembly of actin stress fibers and the translocation of related proteins by releasing mechanical signals, thereby driving the proliferation and differentiation of malignant cells. Under the circumstances, the hard ECM induces tumor cell spreading, pseudopodia formation, and enhances migration ability. To keep the balance, the disorder of these mechanical signals ultimately forms a mechanical trap network: tumor cells accelerate division on hard matrix and actively migrate under pressure gradient. It can be said that mechanical factors are like a hidden clue, connecting key processes such as proliferation, migration and invasion of tumor cells, also drug resistance.

3.2.2. Disordered vascular system

With the uncontrollable proliferation of tumor cells, the expanding tumor mass generates solid stress that compresses blood vessels, resulting in obstructed blood flow and localized hypoxia. Hypoxia triggers stromal release of vascular endothelial growth factor. Subsequent activation of VEGF-2 receptors on adjacent endothelial cells promotes their migration to the region of hypoxia and production of hypoxia-inducible factors 1 (HIF-1) and 2 (HIF-2) [7]. Interstitial fluid dynamics induce vascular wall remodeling through mechanotransducive signaling, particularly during the early stages of angiogenic sprouting. Following endothelial basement membrane disruption, a subset of invasive endothelial cells exhibits directional migration against the interstitial flow vector. This mechanoresponsive behavior results in neo vessel formation initiating within low-shear microenvironments (shear stress <5 dyn/cm^2) and subsequently progressing toward adjacent high-pressure zones (interstitial pressure >15 mmHg), establishing a pressure gradient-guided vascular network architecture [8]. The elevated IFP not only impedes the penetration of chemotherapeutic agents but also propels tumor cells to migrate towards normal tissues with lower pressure. Furthermore, the blood flow shear stress in disordered blood vessels fluctuates between high and low. The high shear stress increases vascular permeability, leading to the extravasation of fluids and cytokines. when tumor blood vessels rupture or blood flow accelerates suddenly, transient high shear stress can compromise vascular integrity and trigger endothelial cell damage. Under sustained high fluid shear stress (FSS) stimulation, blood vessels undergo significant structural remodeling, which facilitates the formation of a tumor-promoting microenvironment through enhanced angiogenesis and ECM remodeling, thereby providing essential nutrients and oxygen to support neoplastic progression

[9]. In regions with slow blood flow, low shear stress activates the pro-angiogenic phenotype of endothelial cells. While diminished shear stress induces pathological angiogenesis to nourish the tumor.

3.2.3. Tumor immune microenvironment

The stiff matrix generated by the dense ECM forms a physical barrier that impairs the effective migration of T cells into the tumor core. Combined with the fluid resistance caused by vascular permeability and lymphatic reflux, this directly hinders T cell extravasation and movement from blood vessels to tumor areas. ECM stiffness also modulates the expression of immune checkpoint molecules on tumor cell surfaces. By binding to PD-1 receptors on T cells, it suppresses T cell immune responses, enabling tumor cells to evade immune attacks. Additionally, solid stress compresses blood vessels, leading to hypoxia and acidosis. Hypoxia-inducible factor-1α (HIF-1α) mediates tumor cell survival and proliferation through its vascular endothelial growth factor (VEGF)-mediated angiogenic activity, with pharmacological suppression of this transcription factor effectively disrupting metastatic dissemination [10]. Acidic extracellular pH environments induce transcriptional activation of oncogenic factors including VEGF and interleukin-8 (IL-8) via pH-dependent regulatory mechanisms in tumor cell populations [11]. This directly inhibits the cytotoxicity and proliferative capacity of CTL and NK cells while inducing massive production of immunosuppressive factors such as adenosine, driving the microenviroment towards an immunosuppressive direction.

3.3. The Systemic Effects of Mechanical Signals in the Tumor Microenvironment

3.3.1. Malignant proliferation and survival regulation

Mechanical signals activate pro-proliferative pathways such as ERK2/MAPK through phosphorylation cascades, promoting cell cycle progression, proliferation-related gene expression, and pro-tumorigenic factor production, thereby accelerating proliferation. Intravascular shear stress and interstitial fluid flow can either promote or inhibit proliferation by modulating tumor cell morphology and signaling pathways (such as PI3K/Akt pathways). Furthermore, excessive mechanical compression induces adaptive proliferation through stress pathway activation, while decompression often triggers compensatory proliferative responses.

3.3.2. Tumor invasion and metastasis

Tumor invasion and metastasis is also a complex process, involving local invasion of the basement membrane and cell migration. The hard ECM activates mechanosensitive ion channels, causing changes in calcium ion concentration, which enhances migration ability by forming lamellipodia and stress fibers through dense actin networks. Meanwhile, stiff ECM promotes tumor cells to release degrading enzymes such as matrix metalloproteinases, damaging basement membrane components. The dense actin network supports tumor cell migration by forming lamellipodia and stress fibers parallel to the long axis of the cell body [12].

3.3.3. Drug resistance and Immune escape

Changes in ECM hardness in the tumor microenvironment are closely related to tumor drug resistance. Increased ECM stiffness can over-activate integrin signaling pathways in tumor cells, reduce drug-induced apoptosis efficiency, which not only hinders the effective delivery of therapeutic drugs within tumors but also enhances tumor cells' drug efflux capacity, promoting the development of tumor drug resistance. The most cunning aspect of tumors lies in their ability to domesticate the immune system: elevated IFP pushes T cells out of the tumor core area, preventing them from contacting cancer cells. The stiff ECM forces macrophages to transform into immunosuppressive M2 type, while up-regulating PDL1 expression in tumor cells, rendering T cells unable to mount an attack.

4. Mechanical Property Characterization Techniques and Clinical Translational Capability

Microfluidic chip technology is based on fluid mechanics and utilizes microchannels to simulate the microvascular environment. In micron-scale channels, the fluid Reynolds number of the fluid is extremely low, with viscous forces far exceeding inertial forces. As a result, the fluid exhibits stable laminar flow. When multiple fluids flow in parallel, instead of turbulent mixing, substance exchange occurs solely through molecular diffusion. This characteristic makes it particularly suitable for high-throughput screening and precise concentration gradient generation in monitoring of mechanical indices. Microfluidic chip technology can also integrate multiple functional units. By precisely controlling microscale fluid flow, mixing, separation, and reaction processes, it realizes the miniaturization and automation of biological and chemical operations.

4.1. Early Detection and Recurrence Diagnosis

During the early stages or recurrence of cancer, biological samples such as circulating tumor cells (CTCs), secretions, and tissue cells undergo specific alterations in mechanical properties. Microfluidic chips can effectively capture and isolate these samples, enabling quantitative analysis of their mechanical parameters and combine with atomic force microscopy (AFM) to detect CTC stiffness (<1 kPa), allowing malignant tumor grading. The approach demonstrates high accuracy and efficiency, addressing the limitations of traditional imaging techniques in detecting early-stage tumors or minimal residual disease. Furthermore, by dynamically monitoring post-treatment changes in CTC stiffness and YAP expression, it provides an early warning system for tumor recurrence. Microfluidic chip also shows great application potential in CTCs capturing due to its multiplexing and simplicity. Various CTCs isolation platforms based on microfluidic chips have appeared one after another, such as CTC-chip, CTC-ichip, spiral chip, GEDI and so on [13].

4.2. Mechanical Model Construction and Personalized Drug Screening

Microfluidic chip can construct organoid micromodels to simulate the microenvironment during disease progression. These platforms allow continuous monitoring of mechanical property alterations (stiffness gradients, interstitial fluid pressure) within cellular architectures through integrated biosensors. By incorporating AI algorithms to analyze chip-derived mechanical parameters (stiffness/stress) alongside drug response data, this technology establishes correlations between mechanical properties and targeted drug sensitivity to guide clinical treatment selection. Patient-specific tumor models are developed to mimic tumor stiffness gradients and hypoxic microenvironments, enabling evaluation of drug penetration efficiency. On-chip co-culture systems integrating tumor cells can investigate the synergistic effects of anti-angiogenic agents and immune checkpoint inhibitor. High-throughput microfluidic screening platforms further simulate combined "stiffness gradient + IFP + FSS". This integrated system allows precise evaluation of impacting efficiency of combined therapies targetin. The microfluidic chip supports pharmaceutical companies in identifying novel anti-mechanical resistance drugs, such as Piezo1-targeted inhibitors and CAFs contraction inhibitors, contributing to shorten drug development cycles and improve the success of clinical translation. While traditional 2D cultures fail to adequately simulate the mechanical microenvironment, leading to many drugs being ineffective in clinical condition. Compared with 2D cell culture, the three-dimensional (3D) cancer cell culture, including 3D hydrogel and 3D spheroids, can better mimic TME, especially the 3D spheroid, which exhibits the complex cellular heterogeneity and the physiologically relevant cell-cell and ECM interactions [14].

4.3. Exploration and Pathways of Emerging Therapeutic Approaches

In tumor therapy, the precise construction of biomimetic microenvironments and multitargeted collaborative intervention strategies have emerged as pivotal approaches to overcoming limitations of conventional therapies. Enhanced Biomimicry leverages synergistic integration of 3D bioprinting

and microfluidic platforms to fabricate dynamic 4D tumor microenvironments that authentically replicate the structural and mechanical complexity of native tumors. These systems not only capture the mechanical heterogeneity of tumor tissues including ECM stiffness gradients and spatially varying vascular networks but also enable real-time modulation of angiogenic factor release and immune cell trafficking, thereby establishing physiologically relevant platforms for drug screening and mechanistic studies. Multitargeted Intervention strategies target critical regulatory nodes within the tumor microenvironment. By incorporating patient-specific microenvironmental characteristics, these approaches dynamically adjust multitargeted drug combinations, providing the potential for precise, adaptive therapeutic regimens.

5. Conclusion

The mechanical properties of the tumor microenvironment constitute crucial non-biochemical regulators of tumor progression, fundamentally characterized by bidirectional remodeling involving decreased cellular stiffness and ECM stiffening, along with mechanical forces including solid stress, interstitial fluid pressure, and fluid shear stress. These mechanical signals are transformed into biochemical cues through integrin-FAK pathways, mechanosensitive ion channels, and cytoskeleton-nuclear Mechan transduction mechanisms, driving malignant progression across multiple dimensions at different aspects, such as the cellular level (modulating proliferation and invasion), tissue level (inducing vascular abnormalities and drug penetration barriers), and systemic level (facilitating immune evasion and drug resistance). Current targeted therapeutic strategies aimed at modulating the mechanical properties of tumor cells and ECM remain in nascent exploratory phases. However, with the in-depth exploration of biomechanical tumor microenvironment, mechanical regulation has demonstrated significant therapeutic potential in oncology. Future advancements are anticipated to yield more precise and efficient biomechanical assessment technologies, providing robust data support for comprehensive investigation of tumor cell and ECM mechanical properties, thereby identifying novel therapeutic targets and strategies to enhance anti-tumor immune responses.

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