Review

Open Access

Check for updates

Mechanical force-mediated interactions between cancer cells and fibroblasts and their role in the progression of hepatocellular carcinoma

Zheng Peng[1],#, Yanling Ding[2],#, Hongyu Zhang[1], Xia Meng[1], Yiyong Huang[1], Pengfei Zhang[3], Zepeng Li[4], Xiaoling Zhou[4]

[1]Department of Clinical Laboratory, Liuzhou Traditional Chinese Medical Hospital, Liuzhou 545001, Guangxi, China.
[2]Department of Clinical Laboratory, Liuzhou Maternity and Child Healthcare Hospital, Liuzhou 545001, Guangxi, China.
[3]Department of Pulmonary and Critical Care Medicine, Liuzhou Traditional Chinese Medical Hospital, Liuzhou 545001, Guangxi, China.
[4]Department of Gastroenterology, Liuzhou Traditional Chinese Medical Hospital, Liuzhou 545001, Guangxi, China.
#Co-first authors.

Correspondence to: Zepeng Li, Department of Gastroenterology, Liuzhou Traditional Chinese Medical Hospital, No. 6 Honghu Road, Liuzhou 545001, Guangxi, China. E-mail: lnnl@163.com; Xiaoling Zhou, Department of Gastroenterology, Liuzhou Traditional Chinese Medical Hospital, No. 6 Honghu Road, Liuzhou 545001, Guangxi, China. E-mail: zxl_lz@163.com

How to cite this article: Peng Z, Ding Y, Zhang H, Meng X, Huang Y, Zhang P, Li Z, Zhou X. Mechanical force-mediated interactions between cancer cells and fibroblasts and their role in the progression of hepatocellular carcinoma. *J Cancer Metastasis Treat* 2024;10:4. https://dx.doi.org/10.20517/2394-4722.2023.137

Abstract

Mechanical forces play a key role in the initiation and progression of cancer. Intercellular interactions between fibroblasts and cancer cells contribute a large portion of the mechanical forces in tumor tissue. Hence, further investigation of the mechanical force-mediated intercellular interactions between cancer cells and fibroblasts is urgently needed, given the slow progress in the management of various solid cancers. In our previous study, we observed obvious mechanical force-mediated interactions between hepatocellular carcinoma (HCC) cells and fibroblasts through integrins and ECM proteins by using our coculture model and discovered that these interactions play important roles in 3D structure formation and tumor growth, suggesting their potential application in HCC treatment. In this review, we summarize the recent research progress in this field in hopes of providing insight into the development of potential anticancer strategies, with a special focus on HCC.

Keywords: Mechanical force, intercellular interactions, fibroblast, hepatocellular carcinoma

INTRODUCTION

A solid tumor comprises not only cancer cells or cancer stem cells but also a heterogeneous group of host stromal cells, an intricate network of extracellular matrix (ECM), and a series of secreted factors, which are known as the tumor microenvironment (TME)[1]. Instead of being considered a silent and passive "bystander", the TME is now believed to be a key promoter of cancer progression through active interactions with cancer cells[2].

From the perspective of physics, on the one hand, uncontrolled growth of solid tumors in confined spaces causes a dramatic increase in compressive pressure on the surrounding TME[3,4]; on the other hand, cancer cells are continuously exposed to mechanical forces in the TME, including compressional and tensional forces[5]. Moreover, many solid tumors, including hepatocellular carcinoma (HCC), share several characteristics, such as the loss of mechanical homeostasis, changes in tissue-level mechanical forces, and the stiffening of pathological tissue[6-8]. Initially, these physical characteristics were perceived as the natural consequences of tumor development until scientists discovered that these mechanical properties could also contribute to many key biological events in tumor progression, such as cancer cell proliferation/survival[9,10] and epithelial-mesenchymal transition (EMT)[11,12]. Since then, mechanical forces have attracted increasing attention in cancer-related studies[13-18]. For example, it has been reported that mechanical forces can direct cancer stem cell behavior during development and metastasis[18].

Mechanical forces stimulate cancer cells through mechanoreceptors, while cancer cells respond by exerting reciprocal forces generated by actin and myosin networks, e.g., myosin-generated contraction; this process is termed mechanoreciprocity[19]. Mechanoreciprocity can maintain tensional homeostasis in tumor tissue, and its loss promotes disease progression, including invasion and metastasis[20]. For instance, scientists initially discovered that cancer cells possess unique mechanical properties compared to their normal counterparts[21]. The TME also has several mechanical characteristics, which could result in disturbances in cellular cytoskeletal tension and mechanosignaling transduction[22,23] and ultimately contribute to malignant transformation, tumorigenesis, invasion, and metastasis[22,24,25].

Among all stromal cells in the TME, cancer-associated fibroblasts (CAFs) are the most abundant cell type[26]. Under normal physiological conditions, fibroblasts are quiescent spindle-shaped cells distributed in the connective tissue of different organs[27]. Nevertheless, they display an activated phenotype in cancerous tissue[28]. Initially, scientists believed that CAFs are activated by secreted factors from cancer cells, as experiments have shown that conditioned medium from cancer cells has similar effects[29]. However, this notion is being questioned by reports showing that physical interactions between stromal cells and cancer cells are also indispensable when fixed tumor cells and conditioned media are used separately[30]. Moreover, maintenance of the myofibroblast phenotype reportedly depends on the mechanical tension within the tissue[31].

In addition to their indispensable role in ECM deposition, degradation, and remodeling, which ultimately changes the mechanical properties of the TME, CAFs have recently been found to also interact with tumor cells by exerting mechanical forces on tumor cells through physical contact[25,32]. Moreover, CAFs can also form adhesive structures with cancer cells, such as focal adhesions and adhesion junctions. Taken together, these findings indicate that CAFs are key regulators of the biological behaviors of tumor cells, such as proliferation, migration, and invasion[33-35]. Hence, understanding the mechanical aspects of these interactions may provide insights into the development of novel therapeutic strategies targeting the tumor microenvironment.

In this review, we focus on the recent progress in mechanical force-mediated interactions between cancer cells and fibroblasts with the aim of providing some insights into their biological basis, the three main generation mechanisms, the conversion of mechanical forces into biochemical signaling pathways, and their main effects on the biological behaviors of tumor cells. In the end, we elaborate on recent related advances in HCC research and introduce our findings during the experiments[36]. We hope that this review will provide a better understanding of related issues and aid in the development of anticancer strategies[37].

THE BIOLOGICAL BASIS OF MECHANICAL FORCES GENERATED BY CAFS AND TUMOR CELLS

In normal tissue, mechanical homeostasis is maintained by many mechanisms, such as growth arrest and contact inhibition[38]. However, during malignancy, cancer cells lose contact inhibition and undergo uncontrolled growth, which disrupts the delicate equilibrium between cell division and cell death (apoptosis), and generates mechanical stress on the surrounding cells[39]. Moreover, by interacting with stromal cells, cancer cells actively remodel the ECM, resulting in increased deposition and crosslinking of fibrous proteins, which eventually hardens the cancerous tissue[40]. As a result, cancerous tissue has a greater elastic modulus than its normal counterpart, as shown in Table 1[41-43]. In this process, fibroblasts are activated into CAFs, which secrete various cytokines and matrix metalloproteinases (MMPs).

Moreover, from the cellular mechanics perspective, due to their key function in connective tissues, compared with other cell types, fibroblasts possess a more organized cytoskeleton that results in distinct mechanical properties, such as stiffer cell bodies and greater contractile forces [Table 2[44-49]]. In addition, fibroblasts exhibit greater mobility than other cells[50,51]. Due to their reorganized cytoskeleton and reduced cell-cell adhesion, cancer cells often have a lower elastic modulus than their normal counterparts [Table 2][52].

Third, scientists recently discovered that CAFs can form mechanically active heterophilic adhesions with cancer cells, as observed in patient-derived material[53], and can exert pulling forces on cancer cells while CAFs contract or migrate. These findings indicate a new mechanical force generation and transduction mechanism in which CAFs can lead cancer cells to invade by traction and dragging, giving rise to a new invasion and metastasis strategy named the "cooperative invasion/metastasis strategy"[53].

Finally, unlike cytokines secreted by cells, ECM proteins secreted by CAFs remain attached to their surface and can form a junction structure called the "fibronexus", which is a specialized focal adhesion complex on the myofibroblast surface, as shown in Figure 1. Since many tumor cells, including liver cancer cells, tend to upregulate integrin expression, they easily adhere to ECM proteins attached to fibroblasts. In this way, these two cell types are connected by ECM proteins, and tensional force is generated and passed to cells connected when fibroblasts contract or migrate[36]. Considering that crosstalk between CAFs and cancer cells, in large part, is carried out through the ECM, the involvement of ECM proteins and integrins in their interactions is highly important.

THREE TYPES OF MECHANICAL FORCE-MEDIATED INTERCELLULAR INTERACTIONS BETWEEN CAFS AND TUMOR CELLS

Mechanical force-mediated intercellular interactions refer to the communication between cells that occurs through the application of physical forces[54]. Mechanical forces can be generated through cell-cell or cell–extracellular matrix interactions and can be transmitted through direct contact or through mechanical signaling pathways[55]. Understanding the mechanisms by which cells sense and respond to mechanical

Table 1. The elastic modulus of normal and cancerous tissues

Category	Liver[42]	Breast[43]	Prostate[43]
Normal tissue	2.3 kPa	1.9-33 kPa	0.8-69 kPa
Fibrotic tissue	5.9 kPa	/	/
Malignant tumor	10.1 kPa	93 kPa	24-100 kPa

Table 2. The elastic modulus of a few common cell types

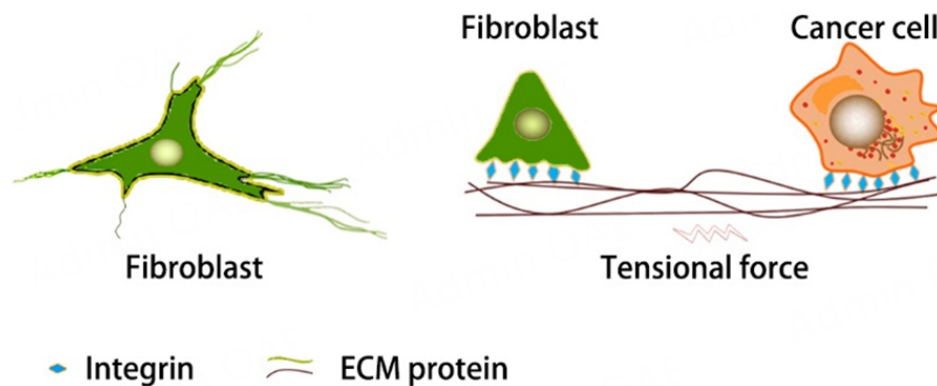| Cell types		Elastic modulus
Fibroblasts		
Embryo	Normal	2.19 kPa[44]
	Activated	5 kPa[45]
	Malignantly transformed fibroblast	0.48 kPa[46]
Fibrosarcoma		0.48 kPa[44]
Liver	Normal	1.18 kPa[47]
	Cancerous	0.3 kPa[44]
Epithelial cells		
Breast	Normal	1.75 kPa[48]
	Cancerous	0.3 kPa[48]
Ovarian	Normal	2.47 kPa[49]
	Cancerous	0.88 kPa[49]

Figure 1. ECM proteins as mediators of mechanical force-mediated interactions between cancer cells and fibroblasts. The left panel shows the tight connection between ECM proteins and fibroblasts, while the right panel shows the mechanical interactions between fibroblasts and cancer cells mediated by ECM proteins. Tensional force is generated as fibroblasts migrate or contract.

forces can provide insights into the regulation of these processes and potentially lead to the development of therapeutic approaches for various diseases[56].

During normal physiological processes, cells are exposed to a variety of mechanical stimuli, including compression and tensile force[57]. Specifically, for CAFs and tumor cells, we summarize three types of mechanical force-mediated intercellular interactions between CAFs and tumor cells, as shown below.

Direct extrusion through ECM remodeling mediated by CAFs (stiffening deposition topology reorganization)

During tumor expansion, a direct extrusion force will be naturally generated due to the limited growth space, as shown in Figure 2[10,58,59]. However, the mechanical stress generated by tumor cells during
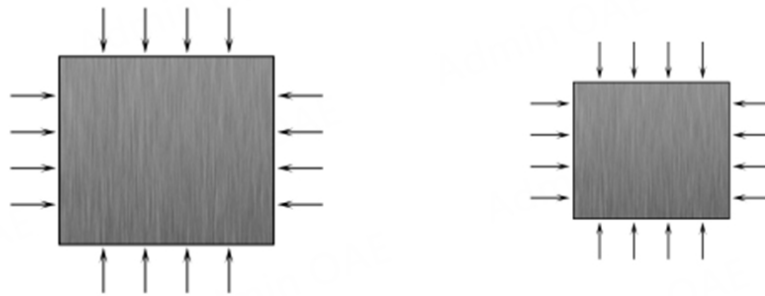
Compression

Figure 2. Diagram depicting the main effects of the compression force applied to tissues/cells. Compression stress is the kind of force applied perpendicularly to the cells, resulting in compaction, which is generated in conjunction with the uncontrolled proliferation of tumor cells[58] or the formation of CAF capsules[59].

expansion depends not only on their growth rate but also on the compliance of the surrounding ECM, in which CAFs play a crucial role[34]. CAFs can change the components of the ECM by specifically upregulating secretion or degradation to affect its rigidity, as suggested by the finding that tumor cells can migrate along fibroblast protrusions[60]. Moreover, the remodeling process generates physical forces that can influence tumor cell behavior[24]. For example, the increased stiffness of the ECM due to CAF-mediated remodeling can promote tumor cell invasion[61] and migration[62].

Indirect intercellular interactions mediated through the ECM and mechanoreceptors
Molecular mechanoreceptors include several families of transmembrane proteins, such as mechanosensitive ion channels and integrins. Mechanosensitive ion channels are ion channels that open in response to mechanical stimuli such as compression or tensional force, as shown in Figures 2 and 3[13]. As another important mechanoreceptor, integrins play a crucial role in mechanosensing and transducing mechanical stimuli into biochemical signals that can be interpreted and responded to by the cell[63]. Moreover, integrins can regulate mechanosensitive ion channels and form macromolecular complexes that help localize the channel to the plasma membrane and regulate downstream signaling proteins such as tyrosine kinases and GTPases[64]. Common ECM ligands of integrins include fibronectin, laminin, and collagen[65]. For example, integrin expression is reported to be much greater in many types of cancer cells than in their normal counterparts. It has been reported that mechanical forces and increased rigidity of the ECM can also upregulate integrin expression[13]. Furthermore, integrin $\alpha_5\beta_1$, in association with fibronectin, has been found to facilitate the differentiation of liver cancer cells and subsequently promote tumor formation and angiogenesis[36].

Heterotypic intercellular interactions (HIIs) mediated by shear forces and N-cadherin
Shear forces or stresses play a critical role in the mechanical aspects of heterotypic intercellular interactions. Shear forces are parallel forces that act in opposite directions, causing one layer of a material to slide or deform with respect to an adjacent layer, which can influence the nature of cell adhesion, migration, and communication[66].

Cadherins are a family of transmembrane proteins that are responsible for mediating cell-cell adhesion and are crucial for the formation and maintenance of adhesion junctions[67]. E-cadherin primarily mediates homophilic interactions within the same cell type, whereas N-cadherin, on the other hand, plays a significant role in facilitating heterotypic interactions. The cadherin interactions between adjacent cells create strong cell-cell adhesion, which helps to maintain the structural integrity of tissues and allows for the
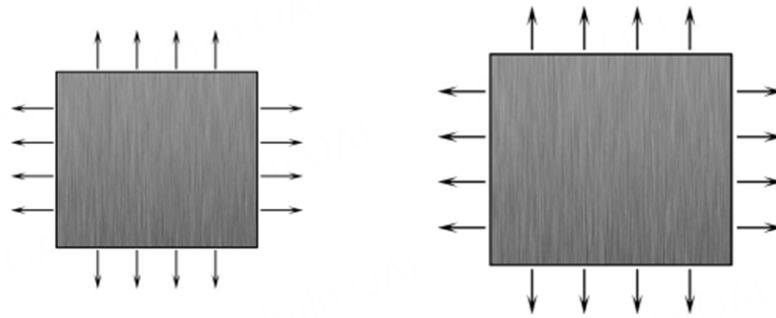
Figure 3. Diagram depicting the main effects of tensional force applied on tissues/cells. Tensional stress is the kind of force applied perpendicular to cells, resulting in expansion, which is usually generated after the formation of adhesion junctions with other cells. In addition to the direct adhesion junctions formed by cadherin, there are indirect adhesion interactions mediated by ECM proteins.

coordination of cell movement and the transmission of mechanical forces[68]. CAFs and other cells can also form heterotypic adhesion junctions with cancer cells via cadherin interactions and lead to collective migration or invasion; CAFs and other cells act as "leaders", as their invasion is followed by cancer cell invasion[69].

MECHANOTRANSDUCTION: FROM MECHANICAL FORCES TO BIOCHEMICAL SIGNALS

Mechanotransduction refers to the biological process whereby cells convert mechanical stimuli or forces into biochemical signals through various mechanisms, including intracellular mechanosensory mechanisms[70]. In addition to the activation of mechanosensitive ion channels, other membrane proteins and intracellular mechanosensory proteins can also play a role in converting mechanical forces into biochemical signals, such as adhesion receptors (integrin, cadherin), cytoskeletal proteins (actin, myosin), and signaling molecules (protein kinases, phosphatases)[71]. Moreover, changes in force distributions across adhesion receptors result in both local and global restructuring of the tensionally integrated cytoskeleton network and cause subsequent biochemical signaling events[72]. Mechanical forces trigger multiple signaling pathways, several of which converge and result in the activation of the GTPase RhoA and downstream consequences of this pathway[73].

Overall, mechanotransduction is a complex process that involves the coordination of the above components that interact with each other to modulate the cellular response to mechanical stimuli[70]. Understanding the above mechanism is essential in various fields, including touch sensation, tissue engineering, and regenerative medicine, as it provides insights into how mechanical forces influence cell behavior, tissue function, and cancer development.

THE MAIN EFFECTS OF MECHANICAL FORCE-MEDIATED INTERCELLULAR INTERACTIONS BETWEEN CAFS AND TUMOR CELLS

As discussed above, mechanical stimuli can be transmitted and converted into biochemical signals through mechanical signaling pathways, which results in a series of biological events and effects, such as proliferation, survival, invasion, migration, and metastasis, as shown in Figure 4[22,74-79]. The major effects are summarized below:

Proliferation
Mechanical forces play a key role in spindle orientation, which is an important event during cell division[80]. Notably, mechanical signaling can also regulate cell proliferation by coordinating focal adhesion assembly
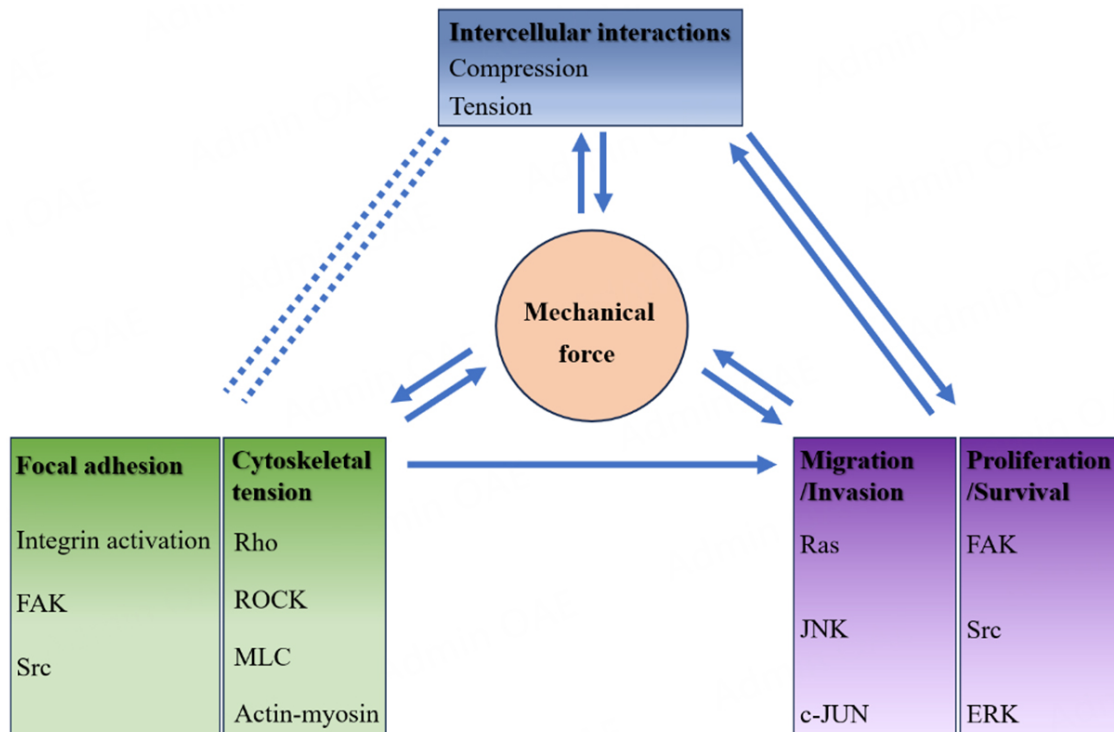
Figure 4. Mechanotransduction of cancer cells in the context of the TME and intercellular interactions and its main effects. Diagram showing the conversion of mechanical forces into biochemical signals within the context of mechanical force-mediated intercellular interactions in solid tumors. Intercellular interactions can be initiated by mechanical forces and can also result in mechanical forces such as compression and tension[83]. Intercellular interactions can be initiated by the proliferation of cancer cells or the migration of connected fibroblasts, and mechanical force-mediated intercellular interactions can also promote the migration, invasion, proliferation, and survival of cancer cells[84]. Mechanical forces can reinforce focal adhesions, stimulate the Rho–ROCK–MLC pathway, and increase cytoskeletal tension[85]. Thus, these reactions will form a self-enforcing (positive) feedback loop. Crosstalk between the FAK-Src-ERK pathway and Rho–ROCK-MLC pathway leads to the activation of ERK and the formation of a FAK-Rho-ERK signaling loop, resulting in increased proliferation and survival[86]. Src is a nonreceptor tyrosine kinase that can activate FAK, which in turn activates RAS and Rho signaling[87]. Rho GTPases, including Rho, are involved in regulating the actin cytoskeleton and cell motility. Rho can activate c-Jun N-terminal kinase (JNK), which is a protein kinase that plays a crucial role in regulating migration, while c-JUN is a transcription factor that is a downstream target of the JNK signaling pathway. Moreover, activation of the JNK signaling pathway can promote metastasis[88].

and reinforcing Rho GTPase signaling[81]. Additionally, mechanical tension causes an increase in cytoskeletal tension, resulting in upregulated extracellular-signal-regulated kinase (ERK) activation[22]. Similarly, indirect mechanical stimuli from ECM proteins increase integrin-related ERK signaling and focal adhesion clustering, which work together with other kinases, such as Src and FAK, to promote tumor cell proliferation and survival. The Hippo signaling pathway is another key regulator of tissue growth, organ size, and cell proliferation[82]. Mechanical signals can impact the Hippo pathway through several mechanisms. For example, when cells experience high mechanical stress or are subjected to increased extracellular matrix stiffness, the Hippo pathway can be activated, resulting in the phosphorylation and inhibition of YAP/TAZ and, as a result, the activation of genes related to cell proliferation and survival[83].

Invasion

Cancer cells detach from a primary tumor, penetrate the surrounding tissue, and invade at the interface, which is a prerequisite for metastasis[84]. As a long-neglected aspect of mechanical force, it is gaining increasing attention[61]. During invasion, mechanical forces can modulate cancer cell motility in the TME with a complex architecture, while in intravasation and extravasation, mechanical forces could modulate the

motility of cancer cells in the vasculature[62]. Moreover, as discussed above, fibroblasts can work with cancer cells and adopt an invasion and metastasis method named the "cooperative invasion/metastasis strategy", in which fibroblasts mechanically pull on the surrounding ECM and open up paths for cancer cells[53].

Moreover, mechanical forces could also promote the invasion of cancer cells in other ways. As previously reported, mechanical compression could facilitate a shift towards an invasive phenotype, in which a subset of cancer cells will extend filopodia at their leading edge[85]. This finding was confirmed by another report that indicated malignant cells actively respond to the mechanical force-mediated stimuli in their TME[86]. Further study revealed that invasion requires dramatic cytoskeleton remodeling, which can also be regulated by mechanical forces provided by the surrounding TME[24]. Another study revealed that changes in ECM components influence key steps in cancer metastasis, such as adhesion, contractility, and motility[61].

Migration/metastasis
Metastasis accounts for more than 90% of cancer-related deaths and usually occurs together with migration after invasion[87]. In addition to genetic factors, the mechanical force-mediated physical interactions of cancer cells with the TME are another key determinant of the metastatic process[62], since remarkable alterations in the mechanics of malignant cells and their surrounding TME are found during metastasis[88]. Metastasis is a complex process involving the activation of various cellular signaling pathways, including the JNK and c-JUN signaling pathways.

RECENT RELATED ADVANCES IN HCC
Specifically, for liver cancer, scientists have shown that mechanical force-mediated intercellular interactions also occur between fibroblas61ts and liver cancer cells[32,53]. In our related research project[36], to observe the direct mechanical interactions between liver cancer cells and fibroblasts, first, we labeled the two cell types with different fluorescent proteins by using lentivirus for live-cell imaging (liver cancer cells with tdTomato, red; fibroblasts with clover, green); second, we adopted the direct coculture method to study their physical intercellular interactions by live-cell imaging. Then, we observed that these two types of cells formed a 3D microstructure with a height of about 80 µm on day 10 [Figure 5A]. However, the height fluctuated around 35 µm for monocultured HepG2-tdT cells and 20 µm for MEF-clover cells, respectively, on day 10 [Figure 5B and C]. Importantly, in immunofluorescence (IF) staining, when we labeled HepG2 cells with species-specific integrin-α_5 antibodies (which recognize only human antigens) to examine the microstructures after fixation and permeabilization, we observed obvious signs of mechanical forces, as indicated by the severely deformed tumor cell contours (as shown by the white arrows in Figure 5D). Combined with the presence of fibronectin and the distribution of fibroblasts (as shown by the typical nuclei in Figure 5D), these results clearly prove the occurrence of mechanical force-mediated intercellular interactions between these two cell types during coculture. Hence, we propose that after binding with fibronectin from fibroblasts, cancer cells are dragged by mechanical forces generated as fibroblasts migrate or contract (as demonstrated in Figure 1). In our further experiments, the administration of (±)-blebbistatin (a potent and selective inhibitor of myosin II ATPase) obviously abolished the formation of 3D microstructures (data not shown). All these results showed the indispensable role of intercellular mechanical forces in intercellular interactions between fibroblasts and liver cancer cells.

Apart from direct interactions, fibroblasts can also exert their influence by actively being involved in ECM remodeling[89], which changes the stiffness or viscosity of the ECM; subsequently, these changes in substrate properties influence the behavior of HCC cells[90]. Moreover, researchers have shown that, compared to normal hepatocytes, liver cancer cells have distinct lifetimes of binding to the substrate, which might explain their differences in cell spreading and motility within diseased tissue[91].
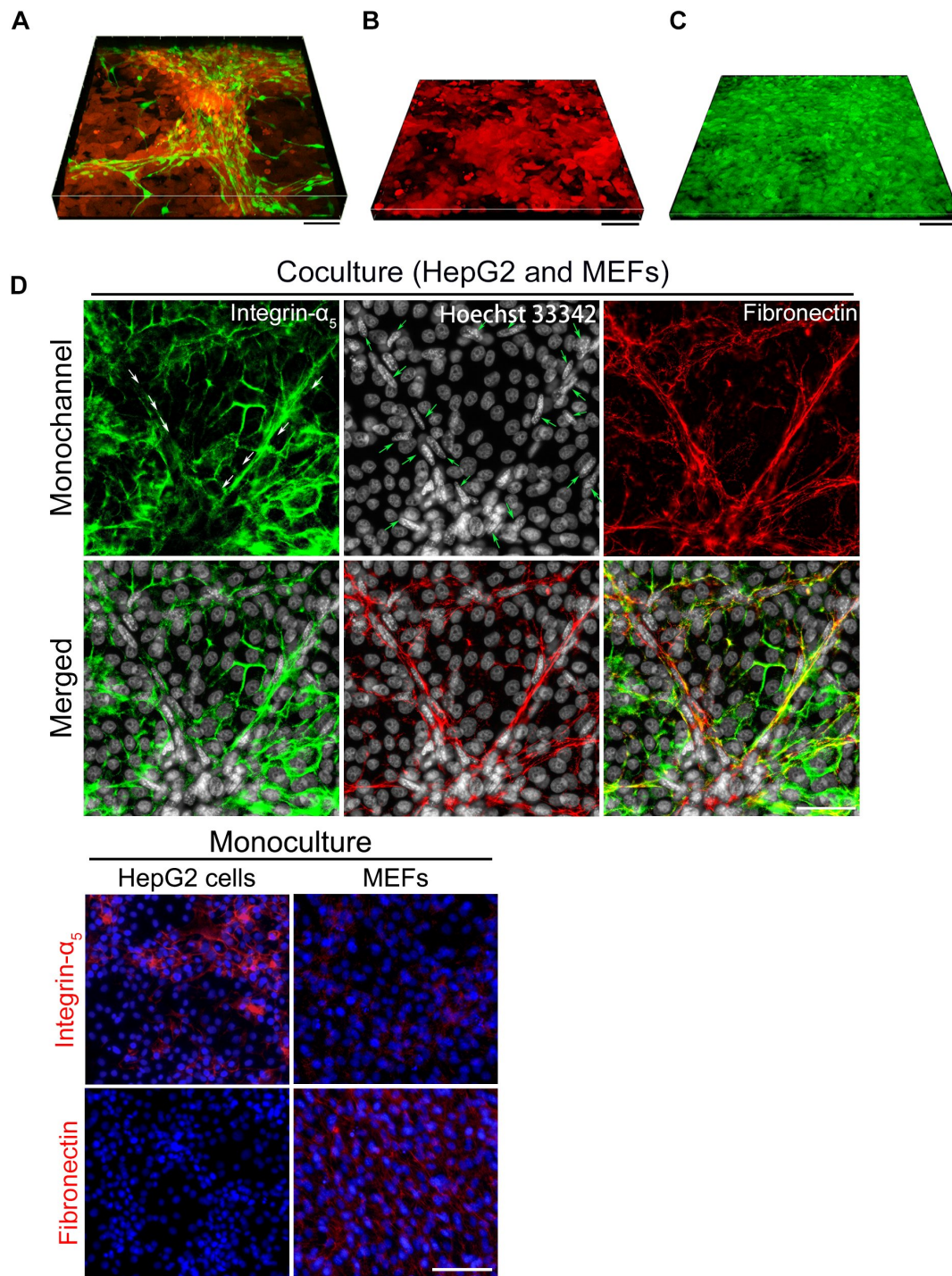
Figure 5. Evidence for the existence and effects of mechanical forces between fibroblasts and liver cancer cells in coculture. (A) Representative fluorescent live-cell image showing the 3D microstructure generated by the coculture of liver cancer cells and fibroblasts on day 10. HepG2-tdT cells (red) and MEF-clover cells (green) were plated together in a confocal dish at a ratio of 1 to 1. Scale bars, 100 μm. (B) Representative fluorescent live-cell image showing the 3D microstructure generated by monocultured HepG2-tdT cells on day 10. Scale bar, 100 μm. (C) Representative fluorescent live-cell image showing the 3D microstructure generated by monocultured MEF-clover cells on day 10. Scale bar, 100 μm. (D) Representative IF staining images of integrin-α_5 (human antigens only), fibronectin, and nuclei in the coculture of HepG2 cells and MEFs. HepG2 cells and MEFs were plated together in a 6-well plate at a ratio of 1 to 1. Sterile coverslips were first placed in each well before plating. IF staining images of monocultured cells are provided below. Scale bars, 50 μm. Figures are modified with permission from Ref.[36] © (2022) the Ivyspring International Publisher.

OPPORTUNITIES AND PROSPECTS

Understanding that mechanical force is an important determinant and the first and key step in understanding the pathogenesis of cancer naturally leads us to conclude that the loss of the ability to sense, respond to, and adapt appropriately to mechanical forces will eventually lead to malignancy[6].

To investigate mechanical force-mediated intercellular interactions, the development of appropriate models that allow for the measurement of mechanical forces and functional analysis with high resolution is an important prerequisite[92]. To date, many different models have been developed to achieve this purpose, and they are broadly classified into two categories: two-dimensional models and three-dimensional models[93,94]. On the one hand, two-dimensional systems could recapitulate both the architecture and the phenotypical behavior of different cell types with reasonable fidelity to some extent. On the other hand, three-dimensional model systems can be used to study force and its effects on cell behavior in the context of an organized tissue structure *in vitro*. Primary or immortalized cells with synthetic hydrogels are used in these systems to mimic *in vivo* conditions, while protein and polysaccharide concentrations in these gels are manipulated to modify their mechanical properties to approximate the proportional elastic modulus needed[95]. With the improvement of model systems, sooner or later, we will solve the mysteries of mechanical force-mediated intercellular interactions.

CONCLUSION

This review not only summarizes the mechanism underlying the generation of mechanical forces between CAFs and tumor cells but also covers the three main types of mechanical force-mediated intercellular interactions, the conversion of mechanical stimuli into intracellular biochemical signals, and the main effects of these interactions. Considering our latest research findings, we elaborate on the integrin- and ECM-mediated mechanical interactions between liver cancer cells and fibroblasts. Therefore, this review provides valuable insight into the mechanical force-mediated interactions between cancer cells and fibroblasts, especially in HCC.

DECLARATIONS

Authors' contributions
Conceptualized the idea: Peng Z, Ding Y
Provided resources: Zhou X, Li Z
Helped with the resources: Ding Y, Meng X, Zhang P, Huang Y
Wrote the manuscript: Zhang H, Peng Z

Availability of data and materials
All the data utilized in this study are publicly available.

Conflicts of interest
All the authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2024.

REFERENCES

1. Anderson NM, Simon MC. The tumor microenvironment. *Curr Biol* 2020;30:R921-5. DOI PubMed PMC
2. Najafi M, Goradel NH, Farhood B, et al. Tumor microenvironment: interactions and therapy. *J Cell Physiol* 2019;234:5700-21. DOI
3. Yan H, Ramirez-Guerrero D, Lowengrub J, Wu M. Stress generation, relaxation and size control in confined tumor growth. *PLoS Comput Biol* 2021;17:e1009701. DOI PubMed PMC
4. Purkayastha P, Jaiswal MK, Lele TP. Molecular cancer cell responses to solid compressive stress and interstitial fluid pressure. *Cytoskeleton* 2021;78:312-22. DOI PubMed PMC
5. Nia HT, Munn LL, Jain RK. Mapping physical tumor microenvironment and drug delivery. *Clin Cancer Res* 2019;25:2024-6. DOI PubMed PMC
6. Hayward MK, Muncie JM, Weaver VM. Tissue mechanics in stem cell fate, development, and cancer. *Dev Cell* 2021;56:1833-47. DOI PubMed PMC
7. Northey JJ, Przybyla L, Weaver VM. Tissue force programs cell fate and tumor aggression. *Cancer Discov* 2017;7:1224-37. DOI PubMed PMC
8. Ayad NME, Kaushik S, Weaver VM. Tissue mechanics, an important regulator of development and disease. *Philos Trans R Soc Lond B Biol Sci* 2019;374:20180215. DOI PubMed PMC
9. Barnes JM, Przybyla L, Weaver VM. Tissue mechanics regulate brain development, homeostasis and disease. *J Cell Sci* 2017;130:71-82. DOI PubMed PMC
10. Levayer R. Solid stress, competition for space and cancer: the opposing roles of mechanical cell competition in tumour initiation and growth. *Semin Cancer Biol* 2020;63:69-80. DOI PubMed PMC
11. Han SJ, Kwon S, Kim KS. Contribution of mechanical homeostasis to epithelial-mesenchymal transition. *Cell Oncol* 2022;45:1119-36. DOI
12. Wang J, He Y, Yang G, Li N, Li M, Zhang M. Transient receptor potential canonical 1 channel mediates the mechanical stress-induced epithelial-mesenchymal transition of human bronchial epithelial (16HBE) cells. *Int J Mol Med* 2020;46:320-30. DOI PubMed PMC
13. Jang I, Beningo KA. Integrins, CAFs and mechanical forces in the progression of cancer. *Cancers* 2019;11:721. DOI PubMed PMC
14. Martinez A, Buckley M, Scalise CB, et al. Understanding the effect of mechanical forces on ovarian cancer progression. *Gynecol Oncol* 2021;162:154-62. DOI PubMed PMC
15. Bertolio R, Napoletano F, Del Sal G. Dynamic links between mechanical forces and metabolism shape the tumor milieu. *Curr Opin Cell Biol* 2023;84:102218. DOI PubMed
16. Montagner M, Dupont S. Mechanical forces as determinants of disseminated metastatic cell fate. *Cells* 2020;9:250. DOI PubMed PMC
17. Bertero T, Gaggioli C. Mechanical forces rewire metabolism in the tumor niche. *Mol Cell Oncol* 2019;6:1592945. DOI PubMed PMC
18. Bregenzer ME, Horst EN, Mehta P, Novak CM, Repetto T, Mehta G. The role of cancer stem cells and mechanical forces in ovarian cancer metastasis. *Cancers* 2019;11:1008. DOI PubMed PMC
19. van Helvert S, Storm C, Friedl P. Mechanoreciprocity in cell migration. *Nat Cell Biol* 2018;20:8-20. DOI PubMed PMC
20. Butcher DT, Alliston T, Weaver VM. A tense situation: forcing tumour progression. *Nat Rev Cancer* 2009;9:108-22. DOI PubMed PMC
21. Nagelkerke A, Bussink J, Rowan AE, Span PN. The mechanical microenvironment in cancer: how physics affects tumours. *Semin Cancer Biol* 2015;35:62-70. DOI PubMed
22. Jaalouk DE, Lammerding J. Mechanotransduction gone awry. *Nat Rev Mol Cell Biol* 2009;10:63-73. DOI PubMed PMC
23. Young KM, Reinhart-King CA. Cellular mechanosignaling for sensing and transducing matrix rigidity. *Curr Opin Cell Biol* 2023;83:102208. DOI PubMed PMC
24. Li X, Wang J. Mechanical tumor microenvironment and transduction: cytoskeleton mediates cancer cell invasion and metastasis. *Int J Biol Sci* 2020;16:2014-28. DOI PubMed PMC
25. Najafi M, Farhood B, Mortezaee K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J Cell Biochem* 2019;120:2782-90. DOI PubMed
26. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. *Nat Rev Cancer* 2020;20:174-86. DOI PubMed PMC

27.   Dorbala S. Fibroblast activation: a novel mechanism of heart failure in light chain cardiac amyloidosis? *JACC Cardiovasc Imaging* 2022;15:1971-3. DOI PubMed

28.   Kalli M, Papageorgis P, Gkretsi V, Stylianopoulos T. Solid stress facilitates fibroblasts activation to promote pancreatic cancer cell migration. *Ann Biomed Eng* 2018;46:657-69. DOI PubMed PMC

29.   Peng Z, Lv X, Zhang P, et al. Intercellular interactions mediated by HGF and TGF-B promote the 3D spherical and xenograft growth of liver cancer cells. *Curr Protein Pept Sci* 2024;25:71-82. DOI

30.   Chiew GGY, Fu A, Perng Low K, Qian Luo K. Physical supports from liver cancer cells are essential for differentiation and remodeling of endothelial cells in a HepG2-HUVEC co-culture model. *Sci Rep* 2015;5:10801. DOI PubMed PMC

31.   Gerarduzzi C, Di Battista JA. Myofibroblast repair mechanisms post-inflammatory response: a fibrotic perspective. *Inflamm Res* 2017;66:451-65. DOI PubMed

32.   Ansardamavandi A, Tafazzoli-Shadpour M. The functional cross talk between cancer cells and cancer associated fibroblasts from a cancer mechanics perspective. *Biochim Biophys Acta Mol Cell Res* 2021;1868:119103. DOI PubMed

33.   Zhang Q, Peng C. Cancer-associated fibroblasts regulate the biological behavior of cancer cells and stroma in gastric cancer. *Oncol Lett* 2018;15:691-8. DOI PubMed PMC

34.   Ping Q, Yan R, Cheng X, et al. Cancer-associated fibroblasts: overview, progress, challenges, and directions. *Cancer Gene Ther* 2021;28:984-99. DOI

35.   Houthuijzen JM, Jonkers J. Cancer-associated fibroblasts as key regulators of the breast cancer tumor microenvironment. *Cancer Metastasis Rev* 2018;37:577-97. DOI PubMed

36.   Peng Z, Hao M, Tong H, et al. The interactions between integrin $\alpha_5\beta_1$ of liver cancer cells and fibronectin of fibroblasts promote tumor growth and angiogenesis. *Int J Biol Sci* 2022;18:5019-37. DOI PubMed PMC

37.   An J, Hong H, Won M, et al. Mechanical stimuli-driven cancer therapeutics. *Chem Soc Rev* 2023;52:30-46. DOI

38.   Ribatti D. A revisited concept: contact inhibition of growth. From cell biology to malignancy. *Exp Cell Res* 2017;359:17-9. DOI PubMed

39.   Gérard C, Goldbeter A. The balance between cell cycle arrest and cell proliferation: control by the extracellular matrix and by contact inhibition. *Interface Focus* 2014;4:20130075. DOI PubMed PMC

40.   Nia HT, Munn LL, Jain RK. Physical traits of cancer. *Science* 2020;370:eaaz0868. DOI PubMed PMC

41.   Suresh S. Nanomedicine: elastic clues in cancer detection. *Nat Nanotechnol* 2007;2:748-9. DOI PubMed

42.   Venkatesh SK, Yin M, Glockner JF, et al. MR elastography of liver tumors: preliminary results. *AJR Am J Roentgenol* 2008;190:1534-40. DOI PubMed PMC

43.   Wells PN, Liang HD. Medical ultrasound: imaging of soft tissue strain and elasticity. *J R Soc Interface* 2011;8:1521-49. DOI PubMed PMC

44.   Grady ME, Composto RJ, Eckmann DM. Cell elasticity with altered cytoskeletal architectures across multiple cell types. *J Mech Behav Biomed Mater* 2016;61:197-207. DOI PubMed

45.   Rotsch C, Radmacher M. Drug-induced changes of cytoskeletal structure and mechanics in fibroblasts: an atomic force microscopy study. *Biophys J* 2000;78:520-35. DOI PubMed PMC

46.   Park S, Koch D, Cardenas R, Käs J, Shih CK. Cell motility and local viscoelasticity of fibroblasts. *Biophys J* 2005;89:4330-42. DOI PubMed PMC

47.   Evans DW, Moran EC, Baptista PM, Soker S, Sparks JL. Scale-dependent mechanical properties of native and decellularized liver tissue. *Biomech Model Mechanobiol* 2013;12:569-80. DOI PubMed

48.   The Physical Sciences - Oncology Centers Network. A physical sciences network characterization of non-tumorigenic and metastatic cells. *Sci Rep* 2013;3:1449. DOI

49.   Xu W, Mezencev R, Kim B, Wang L, McDonald J, Sulchek T. Cell stiffness is a biomarker of the metastatic potential of ovarian cancer cells. *PLoS One* 2012;7:e46609. DOI PubMed PMC

50.   Mashanov GI, Molloy JE. Automatic detection of single fluorophores in live cells. *Biophys J* 2007;92:2199-211. DOI PubMed PMC

51.   Pelipenko J, Kocbek P, Kristl J. Nanofiber diameter as a critical parameter affecting skin cell response. *Eur J Pharm Sci* 2015;66:29-35. DOI PubMed

52.   Rubtsova SN, Zhitnyak IY, Gloushankova NA. Phenotypic plasticity of cancer cells based on remodeling of the actin cytoskeleton and adhesive structures. *Int J Mol Sci* 2021;22:1821. DOI PubMed PMC

53.   Labernadie A, Kato T, Brugués A, et al. A mechanically active heterotypic E-cadherin/N-cadherin adhesion enables fibroblasts to drive cancer cell invasion. *Nat Cell Biol* 2017;19:224-37. DOI PubMed PMC

54.   Vilchez Mercedes SA, Bocci F, Levine H, Onuchic JN, Jolly MK, Wong PK. Decoding leader cells in collective cancer invasion. *Nat Rev Cancer* 2021;21:592-604. DOI PubMed

55.   Ebrahim S, Liu J, Weigert R. The actomyosin cytoskeleton drives micron-scale membrane remodeling in vivo via the generation of mechanical forces to balance membrane tension gradients. *Bioessays* 2018;40:e1800032. DOI PubMed PMC

56.   Jain RK, Martin JD, Stylianopoulos T. The role of mechanical forces in tumor growth and therapy. *Annu Rev Biomed Eng* 2014;16:321-46. DOI PubMed PMC

57.   Zhang Y, Yu J, Bomba HN, Zhu Y, Gu Z. Mechanical force-triggered drug delivery. *Chem Rev* 2016;116:12536-63. DOI

58.   Broders-Bondon F, Nguyen Ho-Bouldoires TH, Fernandez-Sanchez ME, Farge E. Mechanotransduction in tumor progression: the dark side of the force. *J Cell Biol* 2018;217:1571-87. DOI PubMed PMC

59.   Barbazan J, Pérez-González C, Gómez-González M, et al. Cancer-associated fibroblasts actively compress cancer cells and modulate mechanotransduction. *Nat Commun* 2023;14:6966. DOI PubMed PMC

60.   Miyazaki K, Oyanagi J, Hoshino D, Togo S, Kumagai H, Miyagi Y. Cancer cell migration on elongate protrusions of fibroblasts in collagen matrix. *Sci Rep* 2019;9:292. DOI PubMed PMC

61.   Goldmann WH, Auernheimer V, Thievessen I, Fabry B. Vinculin, cell mechanics and tumour cell invasion. *Cell Biol Int* 2013;37:397-405. DOI PubMed

62.   Wirtz D, Konstantopoulos K, Searson PC. The physics of cancer: the role of physical interactions and mechanical forces in metastasis. *Nat Rev Cancer* 2011;11:512-22. DOI PubMed PMC

63.   Rahaman SG, Mahanty M, Mukherjee P, Dutta B, Rahaman SO. Mechanosensing and mechanosignal transduction in atherosclerosis. *Curr Atheroscler Rep* 2023;25:711-21. DOI PubMed

64.   Wang L, Zheng F, Song R, et al. Integrins in the regulation of mesenchymal stem cell differentiation by mechanical signals. *Stem Cell Rev Rep* 2022;18:126-41. DOI

65.   Graf F, Horn P, Ho AD, Boutros M, Maercker C. The extracellular matrix proteins type I collagen, type III collagen, fibronectin, and laminin 421 stimulate migration of cancer cells. *FASEB J* 2021;35:e21692. DOI PubMed

66.   Inman A, Smutny M. Feeling the force: multiscale force sensing and transduction at the cell-cell interface. *Semin Cell Dev Biol* 2021;120:53-65. DOI

67.   Mège RM, Ishiyama N. Integration of cadherin adhesion and cytoskeleton at adherens junctions. *Cold Spring Harb Perspect Biol* 2017;9:a028738. DOI PubMed PMC

68.   Gloushankova NA, Rubtsova SN, Zhitnyak IY. Cadherin-mediated cell-cell interactions in normal and cancer cells. *Tissue Barriers* 2017;5:e1356900. DOI PubMed PMC

69.   Castellanos-Martín A, Castillo-Lluva S, Sáez-Freire Mdel M, et al. Unraveling heterogeneous susceptibility and the evolution of breast cancer using a systems biology approach. *Genome Biol* 2015;16:40. DOI PubMed PMC

70.   Saini K, Discher DE. Forced unfolding of proteins directs biochemical cascades. *Biochemistry* 2019;58:4893-902. DOI PubMed

71.   Moore SW, Zhang X, Lynch CD, Sheetz MP. Netrin-1 attracts axons through FAK-dependent mechanotransduction. *J Neurosci* 2012;32:11574-85. DOI PubMed PMC

72.   Zuidema A, Wang W, Sonnenberg A. Crosstalk between cell adhesion complexes in regulation of mechanotransduction. *Bioessays* 2020;42:e2000119. DOI PubMed

73.   Lessey EC, Guilluy C, Burridge K. From mechanical force to RhoA activation. *Biochemistry* 2012;51:7420-32. DOI PubMed PMC

74.   Angulo-Urarte A, van der Wal T, Huveneers S. Cell-cell junctions as sensors and transducers of mechanical forces. *Biochim Biophys Acta Biomembr* 2020;1862:183316. DOI PubMed

75.   Li C, Qiu S, Liu X, et al. Extracellular matrix-derived mechanical force governs breast cancer cell stemness and quiescence transition through integrin-DDR signaling. *Signal Transduct Target Ther* 2023;8:247. DOI PubMed PMC

76.   Gaggioli C, Hooper S, Hidalgo-Carcedo C, et al. Fibroblast-led collective invasion of carcinoma cells with differing roles for RhoGTPases in leading and following cells. *Nat Cell Biol* 2007;9:1392-400. DOI

77.   Hebner C, Weaver VM, Debnath J. Modeling morphogenesis and oncogenesis in three-dimensional breast epithelial cultures. *Annu Rev Pathol* 2008;3:313-39. DOI PubMed

78.   Guan X, Guan X, Dong C, Jiao Z. Rho GTPases and related signaling complexes in cell migration and invasion. *Exp Cell Res* 2020;388:111824. DOI PubMed

79.   Xie X, Kaoud TS, Edupuganti R, et al. c-Jun N-terminal kinase promotes stem cell phenotype in triple-negative breast cancer through upregulation of Notch1 via activation of c-Jun. *Oncogene* 2017;36:2599-608. DOI PubMed PMC

80.   Finegan TM, Bergstralh DT. Division orientation: disentangling shape and mechanical forces. *Cell Cycle* 2019;18:1187-98. DOI PubMed PMC

81.   Provenzano PP, Keely PJ. Mechanical signaling through the cytoskeleton regulates cell proliferation by coordinated focal adhesion and Rho GTPase signaling. *J Cell Sci* 2011;124:1195-205. DOI PubMed PMC

82.   Ma S, Meng Z, Chen R, Guan KL. The hippo pathway: biology and pathophysiology. *Annu Rev Biochem* 2019;88:577-604. DOI

83.   Zhang C, Wang F, Gao Z, Zhang P, Gao J, Wu X. Regulation of hippo signaling by mechanical signals and the cytoskeleton. *DNA Cell Biol* 2020;39:159-66. DOI PubMed

84.   Gerashchenko TS, Novikov NM, Krakhmal NV, et al. Markers of cancer cell invasion: are they good enough? *J Clin Med* 2019;8:1092. DOI PubMed PMC

85.   Tse JM, Cheng G, Tyrrell JA, et al. Mechanical compression drives cancer cells toward invasive phenotype. *Proc Natl Acad Sci USA* 2012;109:911-6. DOI PubMed PMC

86.   Mierke CT. The matrix environmental and cell mechanical properties regulate cell migration and contribute to the invasive phenotype of cancer cells. *Rep Prog Phys* 2019;82:064602. DOI

87.   Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: molecular mechanism and potential therapeutic targets. *Semin Cancer Biol* 2020;60:14-27. DOI

88.   Kumar S, Weaver VM. Mechanics, malignancy, and metastasis: the force journey of a tumor cell. *Cancer Metastasis Rev* 2009;28:113-27. DOI PubMed PMC

89.   DeLeon-Pennell KY, Barker TH, Lindsey ML. Fibroblasts: the arbiters of extracellular matrix remodeling. *Matrix Biol* 2020;91-2:1-7. DOI PubMed PMC

Peng et al. J Cancer Metastasis Treat 2024;10:4 **❙** https://dx.doi.org/10.20517/2394-4722.2023.137

90. Ying F, Chan MSM, Lee TKW. Cancer-associated fibroblasts in hepatocellular carcinoma and cholangiocarcinoma. *Cell Mol Gastroenterol Hepatol* 2023;15:985-99. DOI PubMed PMC
91. Mandal K, Gong Z, Rylander A, Shenoy VB, Janmey PA. Opposite responses of normal hepatocytes and hepatocellular carcinoma cells to substrate viscoelasticity. *Biomater Sci* 2020;8:1316-28. DOI
92. Katira P, Bonnecaze RT, Zaman MH. Modeling the mechanics of cancer: effect of changes in cellular and extra-cellular mechanical properties. *Front Oncol* 2013;3:145. DOI PubMed PMC
93. Riehl BD, Park JH, Kwon IK, Lim JY. Mechanical stretching for tissue engineering: two-dimensional and three-dimensional constructs. *Tissue Eng Part B Rev* 2012;18:288-300. DOI PubMed PMC
94. Yang L, Yang Y, Wang S, Li Y, Zhao Z. In vitro mechanical loading models for periodontal ligament cells: from two-dimensional to three-dimensional models. *Arch Oral Biol* 2015;60:416-24. DOI
95. Vedadghavami A, Minooei F, Mohammadi MH, et al. Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications. *Acta Biomater* 2017;62:42-63. DOI