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Review

Application of biomechanics in tumor epigenetic research

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ABSTRACT

The field of cancer research is increasingly recognizing the complex interplay between biomechanics and tumor epigenetics. Biomechanics plays a significant role in the occurrence, development, and metastasis of cancer and may exert influence by impacting the epigenetic modifications of tumors. In this review, we investigate a spectrum of biomechanical tools, including computational models, measurement instruments, and in vitro simulations. These tools not only assist in deciphering the mechanisms behind these epigenetic changes but also provide novel methods for characterizing tumors, which are significant for diagnosis and treatment. Finally, we discuss the potential of new therapies that target the biomechanical properties of the tumor microenvironment. There is hope that by altering factors such as the stiffness of the extracellular matrix or interfering with mechano-sensing pathways, we can halt tumor progression through epigenetic mechanisms. We emphasize the necessity for multidisciplinary efforts to integrate biomechanics with tumor epigenetics more comprehensively. Such collaboration is anticipated to advance therapeutic strategies and enhance our understanding of cancer biology, signaling the dawn of a new era in cancer treatment and research.

1. Introduction

Globally, cancer is the leading cause of death for children and adults under the age of 70. It presents a significant obstacle to increasing life expectancy.[1] Its incidence and mortality rates continue to grow annually. This is based on a comprehensive assessment of the global cancer burden in 2020 for 185 countries or regions by GLOBOCAN. Data shows that in 2020, the risk of developing cancer before the age of 75 was 20.4%, with 9,958,133 cancer-related deaths. The risk of dying from cancer before the age of 75 was 10.7%.[1] The prevalence of malignant tumors profoundly affects various facets of human society. These impacts include detriment to patients' physical and mental health, a decrease in quality of life, sudden escalations in family financial burdens, changes in family dynamics, heightened strain on healthcare systems, and, most tragically for individuals, death.[2,3]

Cancer is a highly heterogeneous disease, with heterogeneity referring to the diversity and complexity cancer exhibits at various levels. Individual tumors and subpopulations of tumor cells can show significant differences in their genetic, histopathological, metabolic, and immunological spectra.[4,5]

Heterogeneity includes intratumor heterogeneity, microenvironmental heterogeneity, and intertumor heterogeneity. Intratumor heterogeneity refers to the presence of different combinations of mutations and gene expression profiles within the same tumor, contributing to genetic heterogeneity. The various components within the tumor microenvironment, such as blood vessels, immune cells, stromal cells, and the extracellular matrix, can influence tumor growth, progression, and response to treatment. Temporal heterogeneity includes the accumulation of genetic mutations, the expansion or disappearance of cell clones, and the development of adaptation and resistance to treatment. Over time, tumors may undergo evolution and change.[6–8]

Different types of cancer exhibit significant differences in clinical

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symptoms and signs. For instance, lung cancer may cause coughing, shortness of breath, and chest pain, whereas liver cancer might lead to abdominal pain, jaundice, and weight loss.[9,10] Understanding and considering different types of cancer is the first step in clinical diagnosis and treatment. The differences among various types of cancer can be observed in genetic characteristics, pathological morphology, and treatment responses. For example, breast cancer can be divided into different subtypes based on the morphology of cancer cells and surface receptors, including Luminal type, human epidermal growth factor receptor 2 (HER2) type, and triple-negative breast cancer. Lung cancer patients with EGFR mutations respond well to EGFR tyrosine kinase inhibitors (EGFR-tkis),[11] while patients with high PD-L1 expression benefit significantly from immune checkpoint inhibitors such as anti-PD1 and anti-PD-L1.[12]

In summary, the development of cancer is a complex, multi-step process influenced by an interplay of genetic alterations and environmental factors. Due to cancer heterogeneity, treatment responses and prognoses vary significantly among different types of cancer and individuals.[6] For example, papillary thyroid carcinoma has a better prognosis and lower recurrence rate,[13] while pancreatic cancer, known as the "king of cancers," has a low survival rate and poor prognosis, with a 5-year survival rate of approximately 2.5%.[14] Additionally, the 5-year survival rate for lung cancer patients is 16%,[15] while small cell lung cancer (SCLC) has a poorer prognosis compared to non-small cell lung cancer (NSCLC), with a 5-year survival rate of about 6%.[16] Different treatment methods also vary among different types of cancer. The Luminal type of breast cancer can be treated with oral endocrine drugs, the HER2 type has specific anti-HER2 targeted therapies, and the triple-negative type only has radio-chemotherapy options. The choice of different treatment regimens also partially determines the survival differences among the various types of breast cancer.[17,18] Therefore, comprehensive histopathological examination, immunohistochemistry, and genetic testing are necessary for different tissue types and even for individual cancers. Treatment plans should be adjusted according to individual conditions at different stages of treatment. More detailed analysis of growth rates, treatment responses, and molecular mechanisms of different cancer types can be found in Table 1.

Early research has categorized the causes of cancer into several key groups: genetic, environmental, biological, immunological factors, and epigenetic modifications. (1) Genetic Factors: Some cancers are linked to specific genetic mutations, such as the increased risk of breast and ovarian cancer associated with mutations in the BRCA1 and BRCA2 genes.[25,26] (2) Environmental Factors: These encompass smoking, alcohol consumption, carcinogens in food, radiation, and specific chemicals.[27] (3) Biological Factors: Various viruses, bacteria, and parasites are implicated in cancer development, with notable examples being the association of HPV with cervical cancer and the hepatitis B virus with liver cancer.[28,29] (4) Immune System Dysfunction: Immunosuppression or immune dysregulation can heighten the risk of developing certain cancers.[27,30] (5) Epigenetic Modifications: Initially referring to inheritable alterations in cellular phenotype without altering the gene sequence, epigenetic modifications involve covalent changes to histones and nucleic acids that regulate chromatin structure and gene expression.[31–33] For instance, studies indicate that the accumulation of epigenetic alterations can lead to the abnormal regulation of tumor suppressor genes and oncogenes, ultimately resulting in the carcinogenesis, progression, and metastasis of hepatocellular carcinoma (HCC).[34]

In the initiation mechanisms of cancer, epigenetic modifications play a pivotal role. These modifications, which include DNA changes, histone alterations, and chromatin remodeling, regulate gene expression without the need for gene mutations.[35,36] Especially noteworthy are those epigenetic modifications that do not involve direct mutations, which have gained increasing attention in recent years for their crucial role in both the onset and progression of cancer.[37,38]

The tumor microenvironment (TME) is an integral component of cancer, comprising both non-cancerous cells and the molecules they produce and release.[39] The TME is marked by features such as heterogeneity, hypoxia, acidic conditions, inflammation, immune suppression, and unique physical properties.[40,41] It contrasts with the conventional tissue microenvironment in its cellular composition, altered physical and mechanical properties, and abnormalities in blood and lymphatic flow.[42,43] These differences can compromise immune surveillance to some degree and foster tumor growth and metastatic progression.[44–46] The TME can be divided into biochemical and mechanical microenvironments, and researchers have conducted in-depth studies in biomechanics in recent years.[43,46] The former pertains to the biochemical components of the TME, while the latter addresses its physical properties. These two microenvironments are not isolated; they interact and together shape the TME, influencing a range of biological processes, including the initiation, growth, and metastasis of cancer.[43]

Biomechanical factors significantly influence tumor initiation, progression, and metastasis.[47] The abnormal physical characteristics of the TME can lead to extensive changes in the epigenome, thereby facilitating the proliferation of cancer cells.[43] The metastatic capabilities of cancer cells are also partly dictated by the physical interactions and mechanical forces within the microenvironment.[35,48] This highlights the intricate

Table 1
Analysis of Growth Rate, Treatment Response, and Molecular Mechanisms of Different Cancer Types.

Cancer type	Common Pathological Subtypes	Growth Rate	Treatment Response	5-Year Survival Rate	Prognosis	Molecular Mechanisms
Lung Cancer[19,20]	Small Cell Lung Cancer (SCLC)	Very Fast	Sensitive to chemotherapy and radiotherapy, but high recurrence rate	6%	Very Poor	TP53, RB1, MYC family gene amplification, NOTCH pathway inactivation
	Non-Small Cell Lung Cancer (NSCLC)	Slow	Poor response to chemotherapy and radiotherapy, good response to targeted therapy and immunotherapy	15–25%	Better prognosis	EGFR, KRAS, ALK mutations
Breast Cancer[21]	Luminal	Slow	Good response to endocrine therapy	70–80%	Better prognosis	ER/PR positive
	HER2+	Fast	Significant response to HER2-targeted therapy	50–70%	Better prognosis	overexpression of HER2 proteins
	Triple Negative Breast Cancer (TNBC)	Fast	Sensitive to chemotherapy, but high recurrence rate	15–25%	Poor prognosis	BRCA1/2 mutations
Pancreatic Cancer[22]	Pancreatic Ductal Adenocarcinoma (PDAC)	Very Fast	Poor response to chemotherapy and radiotherapy	< 5%	Very Poor	KRAS、CDKN2A、TP53 mutations
Liver Cancer[23,24]	Hepatocellular Carcinoma (HCC)	Variable	Good response to surgery and local therapies (early), effective targeted and immunotherapy (late)	10–20%	Poor prognosis	TP53, CTNNB1, VEGF, PDGF signaling
	Intrahepatic Cholangiocarcinoma (ICC)	Moderate to Fast	Good response to surgery, high recurrence rate; limited response to chemotherapy (late)	5–15%	Poor prognosis	IDH1/2, FGFR2, KRAS mutations

relationship between biomechanical factors and tumor epigenetic modifications, shaping the complex nature of cancer.

Recent research has underscored the significance of biomechanics, particularly the mechanical microenvironment of tumors, in cancer progression and treatment.[49] The role of biomechanics in cancer prediction, diagnosis, and treatment is rapidly evolving, such as influencing tumor growth and metastasis by altering epigenetic modifications. However, comprehensive literature reviews addressing the application of biomechanics in tumor epigenetics remain absent. Consequently, by delving deeper into the mechanisms by which biomechanics affects epigenetic modifications in tumors, we can establish a foundational basis for targeted cancer therapies. Investigating and delineating the characteristics and variations of tumors concerning epigenetic alterations from a biomechanical standpoint provides innovative approaches and techniques for the early detection and diagnosis of cancer.

2. Tumor mechanical microenvironment (TMME)

We have come to understand that the TME plays a pivotal role in the initiation and progression of cancer. This microenvironment is characterized by unique physical properties, including elevated solid stresses, increased interstitial fluid pressure (IFP), altered tissue stiffness, and variations in matrix architecture and cell geometry. These physical attributes significantly impact the tissue cells and their surrounding milieu, recruiting normal cells, altering the matrix composition, thereby laying the groundwork for tumor development and affecting the response to therapeutic drugs.[50,51] (Fig. 1).

Solid stress refers to the mechanical forces contained and transmitted within solids and elastic elements, such as compressive, tensile, and shear forces.[52] Elevated compressive and tensile solid stresses arise from cell proliferation, matrix deposition, cellular contraction, and aberrant growth patterns. Factors like rapid cellular growth, abnormal growth patterns, the accumulation of extracellular matrix (ECM) components and fluids, and matrix deposition all contribute to the increase in compressive and tensile solid stresses.[53]

Fluid stress encompasses the mechanical forces present and conveyed within fluid components, such as pressure, shear force, and tension. In most normal organs, IFP approximates zero due to the equilibrium created by regular blood flow and lymphatic drainage. However, in the TME, the increased IFP is attributed to the high permeability of abnormal blood vessels, dysfunctional lymphatic vessels, and the compressive forces exerted on blood and lymphatic vessels by solid stresses. This elevation in IFP consequently induces the flow of interstitial fluid at the tumor periphery.[53,54] Simultaneously, fluid movement within the TME generates shear forces, predominantly affecting endothelial cells that relay these mechanical signals. The tumor's atypical vascular structure, through which blood and lymph flow, creates unique shear stress different from that in normal tissue microenvironments.[43,55]

Stiffness is defined as the resistance of a material to deformation under quasi-statically applied forces, representing an intrinsic material characteristic of the tissue. As a tumor develops, the inherent equilibrium of the ECM becomes disrupted: the overall protein content of the TME rises, fiber cross-linking intensifies, the cytoskeleton undergoes restructuring, and the ECM experiences remodeling. These changes culminate in increased ECM stiffness.[56,57]

In adult tissues, each cell is influenced by its immediate microenvironment, including its composition and geometric shape, which is crucial for maintaining internal equilibrium, transformation, and morphogenesis. As a tumor develops, both it and the surrounding normal tissue undergo structural disruption in a continuous and dynamic process, disrupting the original state of stability. Excessive cellular overcrowding, increased proteolytic activity, and alterations in the extracellular matrix production affect interactions between cells and the matrix, as well as among cells themselves, sending signals that prompt morphological changes. Furthermore, cellular contraction, matrix deposition, and cross-linking also lead to alterations in tissue structure.[53]

These physical properties interweave and interact with each other. For instance, the increase in fluid stress within a tumor is a consequence of solid stress compressing blood and lymphatic vessels. The tensile effect of solid stress leads to the stretching and alignment of the cellular matrix, thereby augmenting the stiffness of the tumor to a certain extent. The flow of fluid activates fibroblasts, which in turn heightens solid stress and stiffness, culminating in changes to the structure of the ECM and similar effects.[53,58]

However, these altered mechanical properties in the TME aren't just passive byproducts of tumor evolution. They actively feedback into the entire cancer system. Their close ties with the physical and biochemical traits of the TME significantly influence tumor and matrix cell behavior throughout cancer progression, collectively determining the tumor's trajectory.[59–61]

3. Cancer and epigenetics

Cancer is a dynamic disease driven by persistent genetic and epigenetic changes.[62] The occurrence, progression, and metastasis of cancer

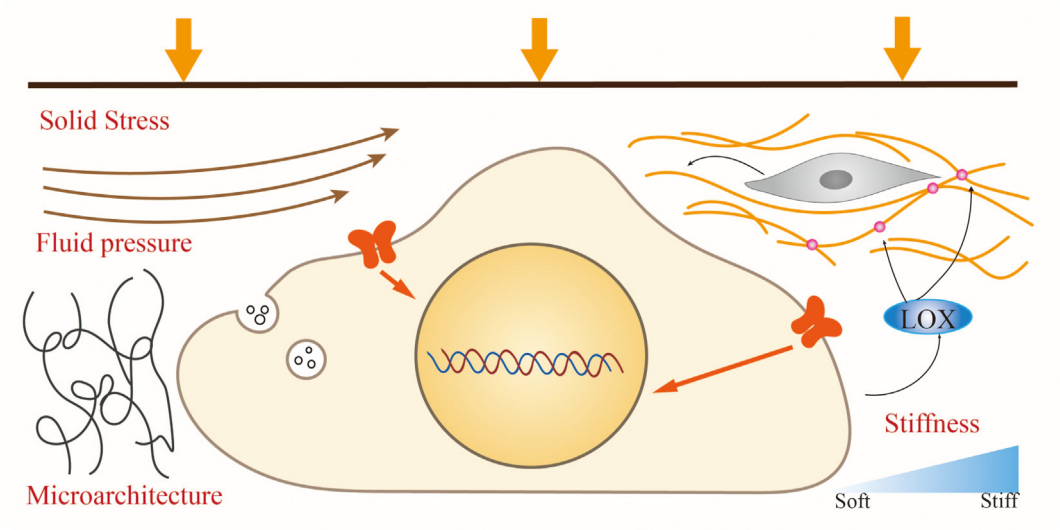

Fig. 1. The physical properties of tumor microenvironment. The physical properties of TME, including solid stresses, fluid pressure (IFP), tissue stiffness, and microarchitecture.

can be driven by two main mechanisms: genetic mutations and epigenetic changes. Genetic mutations drive the clonal selection and evolution of cancer cells, which is a major cause of tumor heterogeneity.[63] Cancers associated with genetic mutations often respond significantly to targeted therapies. For example, NSCLC with EGFR mutations responds well to EGFR inhibitors such as erlotinib and osimertinib.[64] However, this also has a major drawback – the development of drug resistance. The development of drug resistance leads to a decline in long-term survival rates of patients, posing a challenge for new drug development. Epigenetic changes, on the other hand, typically affect multiple genes and signaling pathways, leading to complex phenotypic changes.

Therefore, the changes caused by epigenetic modifications are equally important. They can influence the malignancy of tumors and interfere with treatments, making the study of these modifications crucial. Understanding the role of epigenetic changes in cancer can provide insights into tumor behavior, help identify new therapeutic targets, and improve treatment strategies. This highlights the necessity for ongoing research in the field of epigenetics to enhance our ability to combat cancer effectively.

Epigenetic modifications related to cancer include DNA modifications, histone modifications (such as acetylation, methylation), nucleosome positioning, and non-coding RNA regulation.[31,65] In cancer, a hallmark of cancer cells is the extensive global loss of DNA methylation and the acquisition of local DNA methylation at CpG-rich sites, leading to the silencing of tumor suppressor genes and the aberrant expression of oncogenes.[33,66] Histone modification, pivotal in cancer progression, can influence genes' active or inactive states through processes like acetylation, methylation, and phosphorylation, thereby governing gene expression.[65,67,68] The positioning and density of nucleosomes in a gene's promoter region can impact its transcription. Incorrect nucleosome placement and spacing might result in aberrant gene activation or suppression.[69] Non-coding RNAs, encompassing microRNA (miRNA) and long non-coding RNA (lncRNA), play essential roles. miRNAs can suppress the translation of their target mRNAs or expedite their degradation, influencing specific gene expressions.[70] Aberrant epigenetic modifications contribute to cancer's onset, evolution, and metastasis.[71] Both the TME's biochemical and physical characteristics can induce epigenetic shifts in cancer or stromal cells, forming a bidirectional cause-and-effect relationship.[45,72] Therefore, epigenetic modifications are an important aspect of tumor behavior.[73,74] (Fig. 2).

Epigenetics affects gene expression without altering the DNA sequence, playing a crucial role in the occurrence and progression of cancer.[75] Research by Fumisato Maesaka et al. found that hypomethylation of the CLDN4 promoter DNA is the cause of CLDN4 overexpression in bladder cancer. This overexpression leads to an increase in non-tight junction CLDN4, which promotes cancer stemness through integrin β1 activation, thereby increasing malignancy potential. This suggests that CLDN4 promoter DNA methylation could be a novel marker for malignant bladder cancer and may be used for developing new therapeutic targets.[75]

Additionally, in NSCLC, common epigenetic modifications include DNA methylation, histone modifications, and non-coding RNA expression. Hypermethylation is associated with genes such as RASSF1A, MGMT, CDKN2A/p16, MLH1, MSH2, APC, and RARB.[76] Methylation of DAPK1 and TUSC3 is associated with improved overall survival (OS), while hypermethylation of RAR is related to longer survival. Abnormal histone modifications are linked to dysregulation of key signaling pathways such as PI3K/AKT/mTOR and Wnt/β-catenin. These epigenetic changes promote cell proliferation, evade apoptosis, and enhance invasiveness by inhibiting the expression of tumor suppressor genes. In cancer treatment, drugs targeting DNA methyltransferases (DNMT) and Histone deacetylase (HDAC) are commonly used. Research indicates that HDAC inhibitors exhibit anticancer activity in NSCLC by inducing apoptosis and causing cell cycle arrest.[76,77]

In recent years, increasing evidence suggests that epigenetics plays a crucial role in regulating the occurrence of liver cancer.[78] Studies have shown that genes such as SOCS1, GSTP1, P16, RIZ1, RASSF1A, CDKN2A, CRABP1, CHRNA3, DOK1, SFRP1, GAAD45a, CDKN2B, and MZB1 are frequently hypermethylated in HCC. The abnormal DNA methylation of these tumor suppressor genes is associated with the occurrence of liver cancer.[79–81] Among these, the methylation status of RIZ1 and GSTP1 genes is specific to HCC, thus they can serve as biomarkers for aiding the

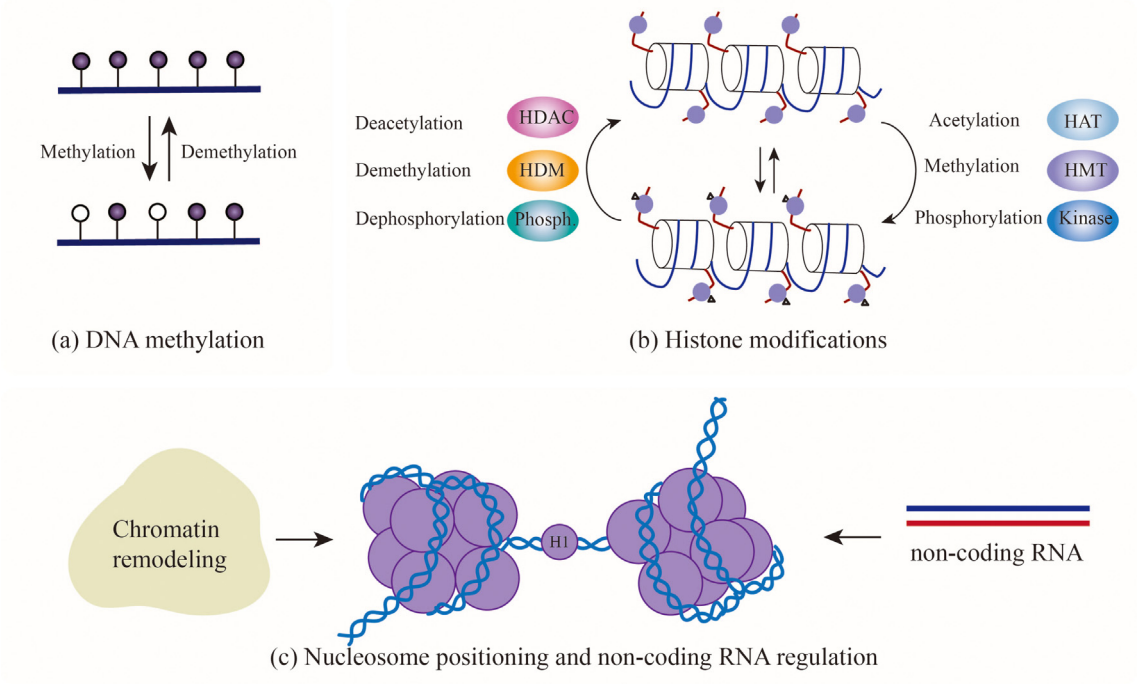

Fig. 2. Cancer-related partial epigenetic modifications. (a) DNA methylation; (b) Histone modifications (including acetylation, methylation and phosphorylation); (c) Nucleosome positioning and non-coding RNA regulation (Chromatin remodeling complexes can slide, disassemble, or rearrange nucleosomes, thus altering their positioning. Certain non-coding RNAs can bind to nucleosomes or histones, affecting their positioning and stability, and consequently influencing gene expression).

clinical diagnosis of HCC.[79] In up to 65% of primary HCC, the suppressor of cytokine signaling 1 (SOCS1) gene is frequently silenced by CpG methylation, indicating that SOCS1 acts as a tumor suppressor in liver cells.[80] In the study by Yu-Xian Liu et al.,[82] the patterns of 11 histone modifications in different types of gene promoters were analyzed, revealing that H3K4me3, H3K27ac, H3K9ac, and H3K27me3 play important roles in oncogene expression in HCC. In the histone modification patterns of different highly and lowly expressed genes (DHLEG), H3K4me3, H3K27ac, and H3K9ac were found to be activating modifications, while H3K27me3 was an inhibitory modification.[82] MicroRNAs (miRs) regulate the expression of various oncogenes and tumor suppressor genes, thereby contributing to the regulation of multiple biological processes, including proliferation, apoptosis, epithelial-to-mesenchymal transition, and metastasis. For instance, the downregulation of miRs let-7g, −22, −26, −29, −99a, −122, −124, −139, −145, and −199b is associated with poor prognosis, increased risk of aggressive tumor recurrence, and shorter disease-free survival. Conversely, the upregulation of miRs 10b, 17–5p, 21, 135a, 155, 182, 221, and 222 is associated with poor prognosis.[83] These epigenetic changes affect the occurrence, development, and prognosis of liver cancer by influencing the regulation of cell proliferation and apoptosis.

Epigenetic changes play a crucial role in cancer progression and therapeutic response. Understanding these changes helps in developing new therapeutic strategies and identifying potential therapeutic targets. Epigenetic regulatory drugs, including DNMT inhibitors, HDAC inhibitors, histone acetyltransferase (HAT) inhibitors, and others, may become important components of personalized therapy in the future.[84] Among these, DNMT inhibitors and HDAC inhibitors have been widely used in cancer treatment.[85]

Various factors, internal and external, can mold the epigenetic state of cancer. These factors range from environmental and genetic to drugs and biomechanics.[60,68,86] Acting individually or synergistically, they induce epigenetic shifts, subsequently influencing gene expression and functionality. The biomechanics' role in cancer epigenetic changes stands out as an important factor for tumor initiation, growth, and metastasis.[87] By manipulating these elements, there's potential to curb crucial stages of tumor evolution. Assessing the mechanical microenvironment's impact on epigenetics can furnish a foundational basis for guiding clinical research and mechanistic studies.

4. Analysis of the mechanisms of biomechanics affecting epigenetic changes

Studies have shown that physical factors in the TME also contribute to cancer progression. An in vitro study by Shalini Menon et al. demonstrated that physical factors contribute to the promotion of existing invasive behaviors in cancer cells, and mechanical signals transmitted from the physical activity of cells within the stroma may enhance cancer progression.[88] Tumor progression is driven by epigenetic modifications, and biomechanical factors influence tumor progression. Understanding whether biomechanical factors affect epigenetic modifications can reveal how mechanical cues influence cell behavior and promote disease progression.

4.1. Mechanical signal transduction

The transmission of mechanochemical signals from the extracellular matrix to the nucleus has become a key feature in regulating cell differentiation and dedifferentiation.[89] Various mechanical signals are detected and transmitted into intracellular mechanisms by activating membrane mechanosensors such as integrins, G protein-coupled receptors (GPCRs), transient receptor potential (TRP) ion channels, mechanosensitive channels, and YAP (Yes-associated protein)/TAZ (transcriptional co-activator with PDZ-binding motif). This activation initiates pathways like GTP-binding protein RhoA, the Hippo pathway, focal adhesion kinase (FAK), JAK/STAT, and PI3K-AKT pathways, ultimately affecting cell behavior. Mechanotransduction converts mechanical stimuli into biochemical signals, altering gene expression or regulating the cytoskeleton and membrane transport, ultimately changing cell function.[90]

Long-distance mechanical effects in living cells are achieved by transmitting forces and vibrational energy through transmembrane integrins and cadherins, associated focal adhesions and junction complexes, and cytoskeletal filaments connecting the nucleus, its internal scaffold, and chromatin. Forces acting on the nucleus may promote changes in the shape, folding, or dynamics of specific load-bearing molecules or alter higher-order chromatin organization, thereby affecting nucleoprotein self-assembly, gene transcription, DNA replication, or RNA processing, which in turn influences cellular epigenetic modifications.[91]

4.2. Cytoskeletal remodeling

Cellular mechanics are primarily controlled by the cytoskeleton, and mechanical forces can lead to the remodeling of the cytoskeleton, composed of microtubules, actin filaments, and intermediate filaments.[89,92,93] Cytoskeletal elements are interconnected by a class of cytoskeletal integrators and connected to the cell membrane and nucleus. Therefore, mechanical forces acting on the cell membrane that cause changes in the cytoskeleton can affect the shape and structure of the nucleus and the spatial organization of chromatin, thereby altering gene expression and epigenetic modifications.[89,91,94]

The nucleus senses changes in substrate stiffness through several proteins, including the LINC (linker of nucleoskeleton and cytoskeleton) complex, which connects the nucleus and cytoskeleton at the molecular level; Nesprin-1, which links the nucleus to the actin cytoskeleton; and YAP and TAZ, which shuttle between the nucleus and cytoplasm in response to mechanical forces dependent on actin cytoskeletal tension to guide transcription factor activity.[89]

Changes in histone modifications, such as acetylation, are associated with changes in nuclear size and shape.[95] For example, a study by Allison B. Chambliss et al. found that cells with relatively high levels of histone H3 acetylation tend to have higher DNA content and higher F-actin content, suggesting that nuclear size and F-actin cytoskeletal content to some extent influence histone H3 acetylation.[96]

4.3. Chromatin remodeling

Chromatin remodeling is the process by which chromatin remodeling complexes (remodelers) and other chromatin factors control the organization of chromatin through the complete or partial repositioning of nucleosomes.[97] Mechanical stress can induce chromatin remodeling through a series of complex biochemical and structural changes, thereby regulating gene expression.

A study by Huy Quang Le et al. found that in epidermal stem cells, mechanical stress exerts its effects through a force-sensing complex composed of emerin (Emd), non-muscle myosin IIA (NMIIA), and actin. Mechanical stress causes Emd to accumulate on the outer nuclear membrane, accompanied by the recruitment of NMIIA, which promotes local actin polymerization and reduces nuclear actin levels. Consequently, heterochromatin cannot effectively anchor to the nuclear lamina, leading to structural changes, specifically the conversion of H3K9me2,3 marks to H3K27me3 marks. Mechanical stress also induces large-scale chromatin rearrangements, relocating certain chromatin regions from the nuclear lamina to the nuclear center. This remodeling results in tighter chromatin compaction, enhancing gene silencing. Additionally, under mechanical stress, PRC2 catalyzes the methylation of H3K27 through its methyltransferase activity, further reinforcing the gene silenced state.[98]

4.4. Regulation of epigenetic modifying enzymes

Mechanical forces can regulate the expression and activity of epigenetic modifying enzymes such as DNMT and HATs, which are directly involved in DNA methylation and histone modifications.

An in vitro experiment by Yi-Zhou Jiang et al. on human arterial and umbilical vein endothelial cells (HAECs and HUVECs) found that under disturbed flow conditions, the expression of DNMT1 and DNMT3A increased and localized to the nucleus, leading to hypermethylation of specific gene promoter regions. In contrast, under undisturbed flow conditions, DNMT expression and activity were lower, and gene promoter regions maintained lower methylation levels, favoring gene expression. For histone acetylation modifying enzymes, disturbed flow increases the expression and activity of HDACs, inhibiting histone acetylation, leading to tighter chromatin structure and thus inhibiting gene transcription. Therefore, hemodynamic forces can regulate gene expression in endothelial cells through epigenetic mechanisms such as DNA methylation and histone modifications.[99] Although this study did not focus on tumor cells, the findings provide new insights for cancer research.

In summary, biomechanical forces alter the tumor mechanical microenvironment, including the mechanical environment of the cytoskeleton and extracellular matrix, triggering a series of signaling pathways that ultimately lead to changes in epigenetic modifications.

5. The application of biomechanics in the study of tumor epigenetic mechanisms

Biomechanics plays an increasingly significant role in researching tumor epigenetic mechanisms. This interdisciplinary approach uncovers how the mechanical environment impacts the epigenetic regulation of cells. It offers a more comprehensive insight into tumor epigenetic modifications, enriching our understanding of tumor growth, metastasis, and progression.[100] Biomechanical models, Biomechanical measurement tools and In Vitro Simulation of Biomechanics have played a role in exploring the application of biomechanics in the study of tumor epigenetic mechanisms.

5.1. Construction of biomechanical models

Biochemical and physical signals from the ECM strongly influence cell fate, the epigenetic landscape, and gene expression.[101] To capture these interactions, it is crucial to build biomechanical models that consider the mechanical factors of cells, ECM, and fluids. These models simulate the mechanical properties within the TME, aiding in the understanding of how tumor cells interact with their mechanical environment. Additionally, they help predict the epigenetic responses of tumor cells in various mechanical situations, ultimately informing clinical treatments.[102]

Recent advancements in 3D culturing systems, as evaluated by Paradiso, F. et al., simulate the biological, mechanical, and biochemical properties of natural tumor tissues. These models can incorporate diverse cell types and multiple ECM elements, offering mechanical support to tissues and playing a pivotal role in cancer cell invasion. Such systems are invaluable for studying the complex interactions within the TME.[101]

Polacheck, W.K. et al. highlighted the importance of diverse experimental platforms and computational methodologies, including both in vivo and in vitro models, to thoroughly investigate the factors influencing tumor cell migration. They emphasized that high-resolution measurements of tumor mechanical properties, the formulation of multiscale models integrating matrix and cellular mechanics, and the creation of artificial ECMs with tailored mechanical properties significantly enhance our understanding of the link between stiffness gradients and cell migration. Furthermore, models capable of concurrently applying multiple stimuli provide a holistic and authentic perspective on tumor cell migration in vivo, leading to novel strategies to curb tumor cell migration and potentially enhancing cancer therapy effectiveness.[103]

Stylianopoulos, T. et al. utilized a mathematical model to simulate fluid flow and drug transport in tumors. This model quantifies vascular efficiency by assessing the proportion of perfused vessels and the density of functional vasculature, encompassing a percolation network of tumor blood vessels with diameters fixed at 15 μm and pore sizes ranging from 50 nm to 400 nm. By incorporating both preclinical and clinical data, the study underscores the significance of biomechanics in understanding and formulating therapeutic strategies for tumors with atypical vascular structures.[104]

Alisafaei, F. et al. designed a mechanomechanical feedback model to explain the interactions among adhesion, the cytoskeleton, and the nucleus. The local tensile stress generated at contact points between cells and the ECM can regulate nuclear morphology, lamin A/C content, and histone deacetylation levels. These stresses are transmitted to the nucleus through the cytoskeleton, triggering a myosin-dependent mechanism that results in the translocation of epigenetic factors within the cell, revealing related tumor epigenetic modification mechanisms.[105]

Naamah B. and David H. introduced an integrated computational model based on Statecharts that synthesizes 3D space and time to simulate the complex dynamic interactions within tumors and their microenvironment. The model starts with a single cancer cell and captures the bidirectional interactions between tumor cells, vascular endothelial cells, and cancer-associated fibroblasts (CAFs) by describing the independent behavior of each system element. In particular, the model demonstrates the critical roles of oxygen and vascular endothelial growth factor (VEGF) in tumor development. The SimuLife tool is used for real-time visualization of model behavior, meticulously capturing the complex interactions within the tumor microenvironment. This helps researchers better understand and analyze the dynamics of tumor growth, providing in-depth insights into tumor behavior patterns and laying the foundation for further research.[106]

In summary, biomechanical models that simulate the mechanical properties within the TME, considering factors such as cells, ECM, and fluids, are essential for understanding how tumor cells interact with their mechanical environment. These models help elucidate the epigenetic responses of tumor cells under different mechanical conditions, providing critical insights that guide clinical treatments.[103,105]

5.2. Biomechanical measurement tools

The advancement and utilization of diverse biomechanical measurement instruments have rendered the mechanical attributes within oncological systems more conspicuously observable. These instruments furnish pragmatic avenues for the continued investigation and corroboration of biomechanically involved epigenetic modification processes. Consequently, this fosters the progression of research into the epigenetic mechanisms underpinning tumorigenesis.

5.2.1. Atomic force microscopy (AFM)

AFM stands as a potent multifunctional imaging tool, a nanoscale imaging method capable of gauging interaction forces between atoms or molecules on surfaces.[107,108] When paired with other microscopy techniques, AFM can pinpoint and correlate intricate cellular structures, such as receptors and transport proteins. It's employed to visualize and determine the dynamic mechanical attributes of cell surfaces (e.g., stiffness, elasticity) or their mechanical interplay with their surroundings (like adhesion, migration).[109] Through AFM, the link between a cell nucleus's mechanical properties and epigenetic modifications becomes clearer.[110] By assessing the rigidity of the tumor cell nucleus using AFM and comparing it with chromatin modification status, researchers can examine how mechanical stimuli influence chromatin structure and its subsequent effect on gene expression. The microscopic morphology and mechanical properties of the tumor cell nucleus, as determined by AFM, shed light on its association with specific epigenetic states.[101,111,112]

5.2.2. Cell traction force microscopy (CTFM)

CTFM is a technique utilized to quantify the force interactions between a cell and its environment. This technique has gained widespread use for measuring the forces generated by individual cells, facilitating the quantification of traction forces exerted on substrates during cellular processes such as growth, migration, or deformation.[113,114] The method typically requires culturing cells on a soft, deformable substrate, like a polymer gel, within which tiny markers—such as fluorescent beads—are embedded. As cells move or exert force, they deform or stretch the gel substrate, consequently displacing these markers. Microscopic tracking of marker movements allows for the determination of both the magnitude and direction of the forces applied by the cells.[115] In recent years, there has been an increase in studies focused on CTFM. Vorselen. D. et al.[116] have advanced traditional TFM by introducing hydrogel microparticles that serve as cellular stress sensors. These particles are not only mass-producible and deformable but also readily customizable for various applications. A particle-based force-sensing strategy has been developed to probe cell–cell interactions.

CTFM is instrumental in unraveling the impact of mechanical signals on tumor cell behavior and epigenetic states, contributing to a more comprehensive understanding of tumor pathogenesis and offering a vital experimental tool for devising new anti-tumor therapies.

5.2.3. Optical tweezers (OT)

OT are a revolutionary technology that harnesses the radiation pressure of laser beams for the precise manipulation of microscopic particles. This technique enables the capture and fine manipulation of minuscule objects, including cells and intracellular organelles, applying nuanced physical forces for measurement and experimental purposes.[117] In cancer research, optical tweezers are employed to intricately manipulate individual cancer cells, thereby investigating their physical properties and behavioral responses.[118]

At the subcellular level, within the scope of cellular biology, optical tweezers prove invaluable for the observation and manipulation of structures such as cell membranes and organelles. They are pivotal in elucidating cellular processes, which involve tracking signaling pathways, interactions, behavioral patterns, and mechanical properties, including tension, pressure, and stiffness. By emulating natural mechanical stresses, optical tweezers facilitate scientists' understanding of mechanotransduction—the process by which cells perceive and respond to mechanical forces in their milieu. For example, they can exert exact forces to trigger specific cellular responses, like calcium signaling, thus underscoring the responsiveness of mechanotransduction to physiological forces.[118,119]

In tumor biology research, optical tweezers offer an advanced technique to investigate the transmission of mechanical signals and their influence on epigenetic alterations. This enhanced insight is pivotal in propelling the development of novel cancer therapies.

Biomechanical measurement tools can aid researchers in elucidating the influence of mechanical signals within the tumor microenvironment on cellular behaviors, encompassing the modulation of intracellular signaling pathways that potentially alter the epigenetic landscape.

5.3. In Vitro Simulation of Biomechanics

5.3.1. Mechanobiology-on-a-chip

Organoids-on-a-chip and Organs on chips (OoC) serve as advanced functional units for simulating human organ functions in vitro, integrating dynamic mechanical cues with chemical signals to replicate complex three-dimensional organ-like structures. These promising in vitro models are crucial for recreating the intricate interplay between biochemical and biomechanical environments of human tissues.[101,120] Mechanobiology-on-a-chip, specifically, emphasizes the influence of mechanical forces as regulators of physicochemical responses in microphysiological systems, offering a unique platform for examining the effect of mechanical stimuli on the epigenetic modifications in tumor cells.[121] Factors such as matrix stiffness, cellular interactions, and chemical gradients are investigated for their roles in altering DNA methylation, histone modifications, and non-coding RNA expression, thereby enhancing the understanding of tumor progression, invasion, and metastasis.[122]

5.3.2. Microfluidic devices

Complementing this, microfluidic devices are precision tools capable of controlling and manipulating fluids at the microscale.[123–125] They simulate physiological conditions like blood flow and shear forces, which are critical for analyzing cell and tissue behaviors within fluid environments at the micrometer level. The devices provide indispensable technical support for exploring how interstitial flow within the tumor extracellular matrix promotes tumor cell invasion and influences epigenetic changes through mechanical shear forces present in the microenvironment.[126]

Hongyan Xie et al. discussed the use of microfluidic technology for tumor modeling to simulate interactions within tumors and capture the complexity of the TME. Microfluidic devices provide a highly adaptable platform for various experimental needs by controlling characteristics such as matrix structure, stiffness, cell composition, and flow rate. These devices mimic the physical and chemical gradients within the TME, enabling precise studies of tumor-immune dynamics, drug resistance mechanisms, and the efficacy of new cancer therapies. These technologies have been used to study tumor growth, migration, angiogenesis, and metastasis, and can simulate interactions between tumor cells and various TME components such as fibroblasts, stromal cells, and endothelial cells. Furthermore, microfluidic technology can monitor immune cell migration and T lymphocyte activation in real-time, thereby assessing immune therapy responses. This approach not only enhances our understanding of cancer biology but also provides new avenues for personalized medicine by testing individual patients' tumors for their responses to various treatments, achieving better clinical outcomes. Continued development of microfluidic-based “tumor-on-a-chip” models and their integration with advanced technologies such as single-cell RNA sequencing and high-throughput drug screening will further enhance their application value in cancer research in the future.[127]

6. Application of biomechanics in characterizing tumor epigenetic modifications

Tumor epigenetic modifications, such as DNA methylation and histone modifications, influence the expression and function of genes. This leads to alterations in cell behavior and the surrounding microenvironment. These alterations impact the mechanical properties of tumor cells and adjacent tissues, including mechanical stiffness, shear force, cell adhesion force, tensile force, compressive force, and solid stress.[43,56,128] Moreover, studies have shown that the external compression or tensile solid stress of tumor cells may be an independent local cell adhesion force, responding to changes in the stiffness of the nearby matrix[129] , Various mechanical factors interact, collectively shaping the tumor's mechanical microenvironment and influencing tumor behavior (Fig. 1).

The mechanical properties of tumor tissues have potential as biomarkers, aiding in early cancer detection and prognosis assessment.[35] While mechanical biophysics “biomarkers” are not as refined as conventional biochemical indicators like cell proliferation and cell death, employing technology to observe tissue biomechanics in vivo is essential. Techniques like magnetic resonance elastography and ultrasound methods are pivotal in this regard.[56] For early tumor detection, the following mechanical characteristics may serve as crucial indicators.

6.1. Mechanical stiffness

Tumors are typically firmer than the surrounding healthy tissues. For instance, breast cancer tissues are more rigid than the adjacent normal breast tissues, which underpins clinical breast palpation.[49] Many factors

can promote the development of tumor stiffness and fibrosis in the microenvironment, while the increase in mechanical stiffness in turn promotes tumor progression and metastasis.[56] Mechanical stiffness, particularly that of the ECM, has been closely associated with cancer progression. This stiffness can impact the epigenetic state of tumor cells and their immediate environment.[100,130] Research indicates that one reason for heightened tumor stiffness is the induction of collagen cross-linking, which solidifies the ECM. This process enhances focal adhesion, subsequently amplifying PI3 kinase (PI3K) activity and prompting the invasion of epithelial cells activated by oncogenes,[131] Furthermore, an increase in the stiffness of the matrix leads to an upregulation in the expression of Fibronectin 1 (FN1) and Matrix Metallopeptidase 9 (MMP9) in tumor cells, promoting angiogenesis and to a certain extent, facilitating the progression and spread of cancer.[132,133] Mechanics is instrumental in evaluating tumor stiffness. Employing various tools and techniques, such as atomic force microscopy (AFM), unconfined compression test (UCT), magnetic resonance elastography (MRE), and ultrasound elastography (USE), can help measure the hardness of tumor tissues or track changes in cellular stiffness. This provides opportunities for early diagnosis, understanding the tumor's growth phase, and predicting its invasiveness.[49,134,135]

6.2. Solid stress

Solid stress within the tumor microenvironment is a pivotal mechanical element, potentially dictating the trajectory and response of tumor cells.[136] The exploration of its interplay with cancer's epigenetic landscape stands as a vital research avenue. The genesis of solid stress lies in the tumor's very architecture.

Nia, H. T. et al.[129] developed experimental and mathematical frameworks for measuring solid stress. They released the solid stress in a controlled manner using specific geometric shapes. Subsequently, they quantified the deformations induced by the stress through high-resolution ultrasound or optical microscopy. Beyond such empirical approaches, mathematical modeling stands as a potent tool to predict tumors' material attributes, solid stress, and the ensuing release of elastic energy.[129] Such precise modeling is not only instrumental in unveiling novel signaling pathways and therapeutic avenues but also holds promise as a prognostic and diagnostic indicator. Finite element analysis models exemplify this by simulating the biomechanical interactions between tumors and their neighboring tissues. Notably, Whyne, C. M. et al.[137] employed such a model to dissect the influences of tumor dimensions, material characteristics, and loading rates on spinal integrity, specifically targeting metastatic spinal afflictions. Their creation, a two-dimensional axisymmetric finite element model, is a testament to the sophisticated analytical capabilities in oncological biomechanics. This cumulative research underscores the integral role of mechanical factors in cancer progression and highlights the transformative potential of biomechanical models in advancing our understanding and treatment of cancer.

The influence of solid stress on cancer cell biology encompasses the compression and collapse of blood and lymphatic vessels, leading to hypoxia, impeding the delivery and efficacy of chemotherapy, radiotherapy, and immunotherapy, as well as augmenting the invasiveness of cancer cells and stimulating oncogenic pathways in colon epithelial cells. Solid stress exerts an indirect effect on cells by deforming components of the ECM. The nucleus, a mechanically sensitive organelle, responds to solid stress through the activity of nuclear pore complexes and associated proteins, modulating the nuclear import of transcription factors.[53] Consequently, measuring solid stress may serve as a means to characterize aspects of cancer epigenetics. Furthermore, the reduction of tumor cells via anticancer drugs leads to a corresponding decrease in solid stress. Monitoring these changes in solid stress can significantly aid in evaluating the effectiveness of treatments and guiding clinical drug administration.

6.3. Fluid stress

In the tumor microenvironment, due to tumor growth, neovascularization, and other factors, fluid stress may change. These changes in the mechanical environment may affect tumor cells and the surrounding cells. For example, shear stress in the tumor microenvironment may result from blood or lymph flow. Given the imperfect angiogenesis in the tumor microenvironment, new blood vessels might be twisted, irregular, and sometimes more permeable. This leads to varying patterns of blood flow shear stress. Some research suggests that shear stress can influence the migration, invasion, proliferation, and survival of tumor cells. Specific shear stresses might even amplify the tumor cells' metastatic potential.[55,138] Endothelial cells (ECs) experience shear stress generated by blood flow and can transform these mechanical stimuli into intracellular signals influencing cell function. The involved signaling pathways encompass MAPK, NF-κB, and others. Consequently, these signals impact tumor proliferation, apoptosis, migration, permeability, remodeling, and gene expression.[139,140]

In conclusion, the biomechanical properties of tumors reveal key aspects of cancer progression, offering a new perspective for early detection, prognosis assessment, and even treatment of cancer. By delving into the mechanical stiffness, solid stress, and fluid stress of tumor tissues, we gain not only a better understanding of the complex interactions between tumor cells and their microenvironment but also discover how these factors impact the epigenetic state of tumors. These insights broaden our comprehension of the mechanisms behind tumor behavior and provide new strategies for early diagnosis and treatment of cancer.

7. Application of biomechanics in suppressing epigenetic modifications in cancer

Epigenetic modifications are considered one of the primary causes of cancer development.[35] During the formation and development of tumors, alterations in cells and the extracellular matrix contribute to the evolution of the mechanical microenvironment. These mechanical factors influence cancer cells, leading to additional epigenetic changes. Notably, biomechanical factors play a pivotal role in this process.[90,141–143] Cells detect external mechanical signals through mechanical sensors, such as integrins and YAP/TAZ. These signals initiate intracellular signal transduction, resulting in various epigenetic modifications. These include changes in chromatin structure and assembly, DNA methylation, histone modification, and the regulation of non-coding RNAs. These modifications cause cytoskeletal remodeling and changes in cell morphology, which in turn influence cell behavior.[53,60,144] This impacts the progression and metastasis of cancer. Thus, by modulating relevant biomechanical factors or intervening in the mechanical sensing pathway, it becomes possible to inhibit tumor epigenetic modifications, steering the direction of cancer treatment strategies.

7.1. Altering the stiffness of the ECM/solid stress

Tumor solid stress is intricately linked with stiffness, and the increased rigidity of the ECM along with heightened solid stress can propel tumor progression in numerous ways. For instance, this progression is facilitated through the modulation of integrin signaling pathways between tumor cells or stromal cells and the ECM, mediated by mechanical signals.[122,145] Or by initiating processes like the epithelial–mesenchymal transition (EMT), which promotes the invasion and dissemination of cancer cells, leading to tumor metastasis and increased malignancy. This increased rigidity can also diminish the chemosensitivity of cancer cells.[49] Hence, modifying the stiffness of the tumor ECM might influence the epigenetic modifications of tumor cells and present a target for cancer therapy. Solid stress, inherent within the

matrix components, can be mitigated through drugs that degrade these components and reduce fibrosis.[146] For example, employing biomaterials and tissue engineering techniques, such as using enzymes like collagenase for localized degradation of the tumor ECM, or inhibitors like lysyl oxidase (LOX) to prevent ECM crosslinking, can effectively reduce the hardness of the tumor ECM.[53,147,148] Additionally, adjusting the activity of stromal or engineered cells, particularly cancer-associated fibroblasts (CAFs) that secret and remodel the ECM, can effectively modify the characteristics and rigidity of the ECM.[49,103]

7.2. Targeting mechanical sensing pathways with drugs

Tumor cells sense the mechanical properties of the TME through mechanical sensors such as integrins and YAP/TAZ, playing a key role in the interactions between cells and the ECM. Through a series of signaling cascades, they produce tumor epigenetic modifications.[60,149,150] The YAP, a transcriptional regulator sensitive to mechanical stimuli, is governed biochemically by the Hippo signaling pathway and mechanically by factors such as ECM stiffness and shear stress.[60] Therapeutics like FAK, TAZ, and YAP inhibitors that target these sensors or pathways are advancing through various stages of clinical trials. Additionally, mechanical forces, including ECM rigidity and tumor-generated stresses, modulate these signaling pathways, ultimately shaping tumor cell behavior (Fig. 3).[151–154] These insights underpin the development of new cancer treatments that harness the mechanical aspects of tumor biology (More detailed information on biomechanics-related cancer mechanotransduction pathways is found in Fig. 4.)

7.3. Physical intervention therapy

Employing physical techniques can directly or indirectly manipulate cells and tissues to achieve therapeutic outcomes, encompassing the use of physical intervention methods such as acoustic radiation and electric field forces to influence cellular behavior and epigenetic states. This approach includes previously described therapeutic strategies: modifying the stiffness of the ECM and targeting mechanosensory pathways with pharmacological agents, and extends to the adoption of novel biomechanical tools and devices to implement these strategies:[155].

(1) Tumor Treating Fields (TTFields) are non-invasive anti-cancer treatments that employ alternating electric fields to impede the division of cancer cells, a process that is usually achieved by electric field forces affecting the random movement of key macromolecules and organelles responsible for mitosis and cytoplasmic division.[156,157]
(2) High-Intensity Focused Ultrasound (HIFU) is a non-invasive method in which ultrasonic energy has the potential to destroy tissue or enhance drug delivery, eradicating tumors by generating a precise focal point with the resulting acoustic radiation force, among other things. Since HIFU can cause cell death, tissue damage and subsequent repair response, it may induce certain epigenetic changes. However, further studies are needed to explore the specific mechanisms.[158,159] The application of biomechanics in epigenetic modification of tumors is summarized in Table 2.

8. Conclusions and future directions

The intersection of biomechanics and tumor epigenetics has opened innovative avenues to understand and combat cancer. This review discusses how to use biomechanical tools and methods to decipher the complex mechanisms driving tumor epigenetic changes. It elucidates the importance of biomechanics in characterizing tumor epigenetics and delves into its potential therapeutic applications. Based on the current foundation, several prospects should be considered.

1. The complexity of the TME is crucial for understanding cancer progression. Emphasizing the biomechanical properties of the TME offers

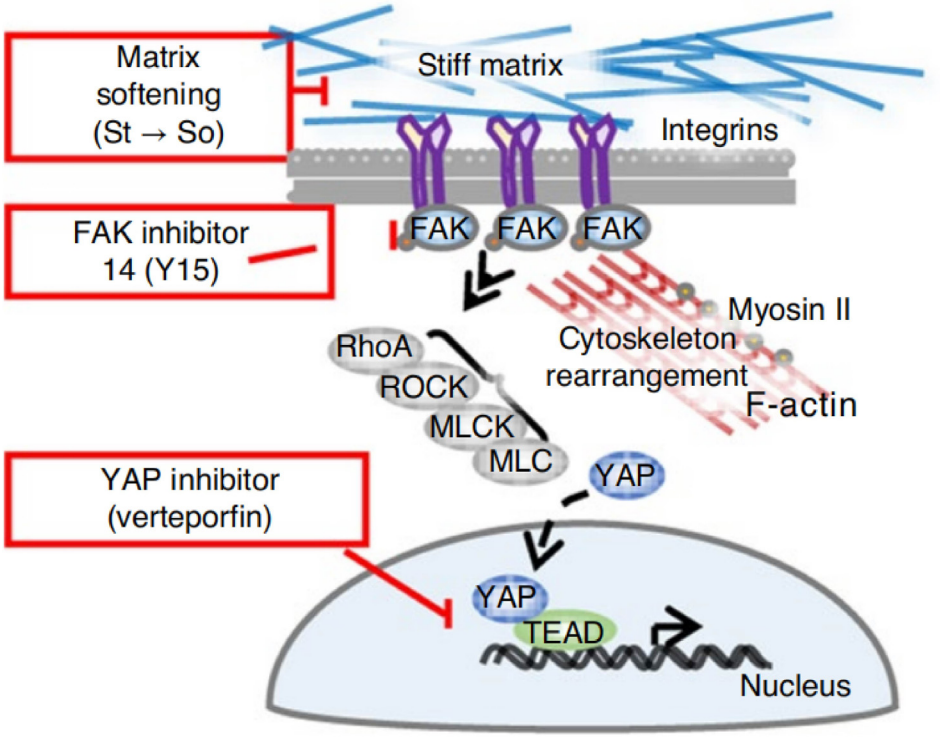

Fig. 3. Biomechanical influences on integrin-TAZ/YAP pathway. Increased ECM stiffness, fluid stress, and solid stress can all potentially influence the integrin-TAZ/YAP pathway. This, in turn, affects the epigenetic modifications in tumors, promoting cell proliferation and inhibiting programmed cell death. As a result, softening the matrix, using FAK inhibitors, and TAZ/YAP inhibitors can inhibit this pathway. Form.[122] Reprinted with permission from AAAS.

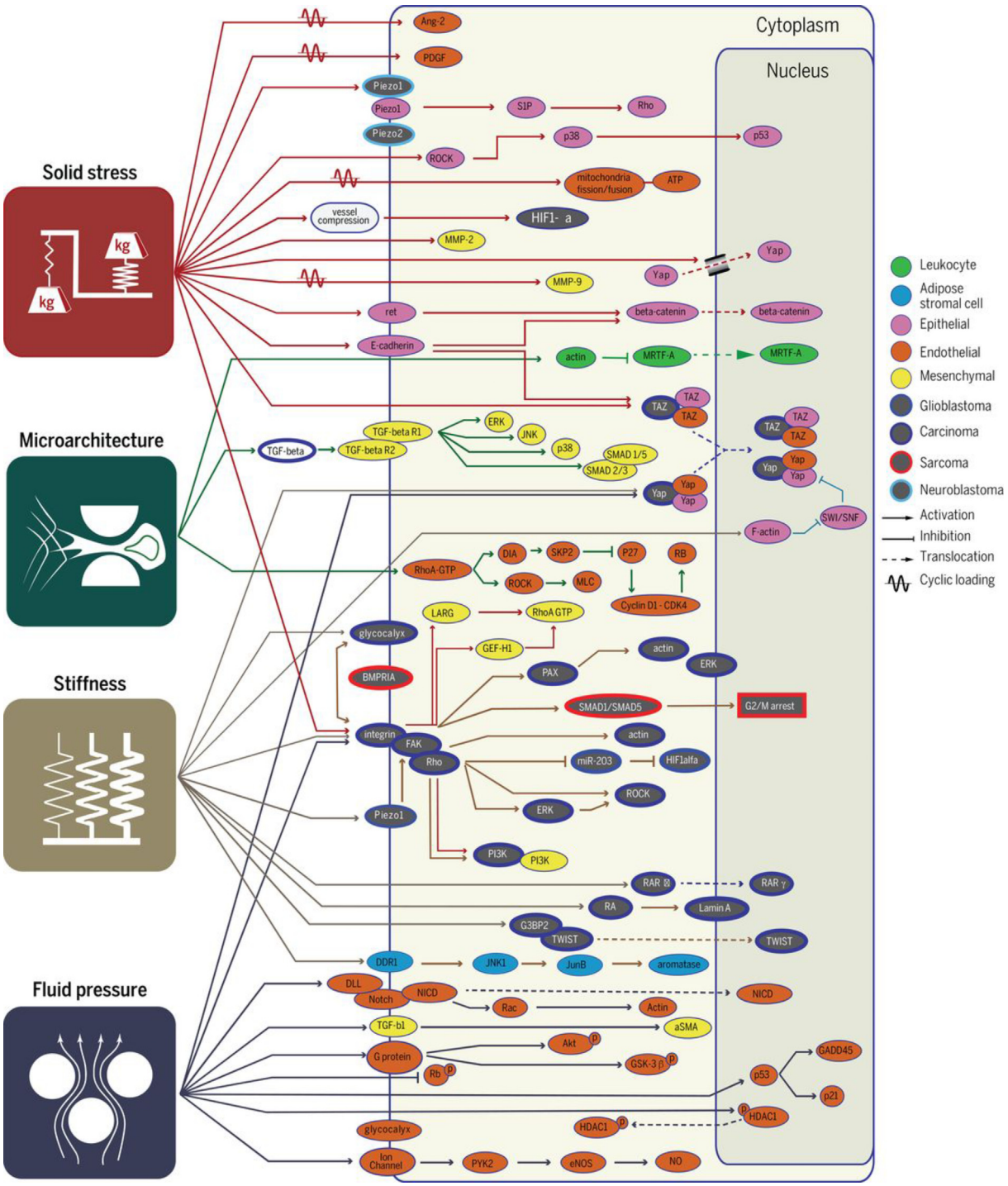

Fig. 4. Biomechanics-related cancer pathways. The physical characteristics of cancer activate numerous mechanoresponsive pathways in cancer cells and stromal cells, including endothelial cells, epithelial cells, mesenchymal cells, and immune cells. Form.[53] Reprinted with permission from AAAS.

an alternative approach to intervening in the cancer process. Modeling the complex interactions within the tumor microenvironment can enhance our overall understanding of cancer dynamics, laying the foundation for understanding cancer dynamics and developing related targeted therapies.

2. Epigenetic modifications play a significant role in the occurrence and development of cancer. Due to tumor heterogeneity, the mechanisms of occurrence, development, and metastasis vary among different tumors. In tumors driven primarily by genetic mutations, gene-targeted therapies have shown unique efficacy. However, epigenetic-based therapies may address the limitations of resistance often seen in targeted therapies. In tumors primarily driven by epigenetic modifications, further exploration of the factors influencing these modifications and their molecular mechanisms is key to understanding and treating this type of cancer.
3. Biomechanical factors influence epigenetic modifications to some extent. Tumor progression is driven by epigenetic modifications and influenced by biomechanical factors. Biomechanical factors may alter tumor growth trends by affecting epigenetic modifications in tumors. Clarifying these mechanisms further could provide new approaches for tumor prevention and treatment.

Table 2
Application of biomechanics to epigenetic modifications of tumors.

Application Field	Specific Tools or Methods	Description	Related Mechanisms	References
Biomechanical Model Construction	3D Culturing Systems	Simulate tumor tissue properties	Study TME interactions	101,106
	Multiscale Models	Integrate matrix and cell mechanics	Predict epigenetic responses under different conditions	103
	Mathematical Models	Simulate fluid flow and drug transport	Assess vascular efficiency and drug penetration	104,105
Biomechanical Measurement Tools	AFM	Measure cell surface mechanics	Link mechanical properties to epigenetic states	107–112
		Measure nucleus rigidity	Correlate with chromatin modifications	
	CTFM	Quantify cell-environment forces	Study impact on cell behavior and epigenetics	113–116
		Measure forces during growth/migration	Quantify traction forces	
	OT	Manipulate microscopic objects	Investigate mechanical signal transmission and epigenetic impact	117–119
		Observe cell membranes and organelles	Study mechanotransduction and cellular responses	
In Vitro Simulation of Biomechanics	Mechanobiology-on-a-chip	Simulate mechanical signals	Study effect on epigenetic modifications	120–122
		Integrate mechanical and chemical signals	Examine matrix stiffness and cellular interactions	
	Microfluidic Devices	Simulate physiological conditions	Analyze fluid mechanics impact on cell behavior and epigenetics	123–127
		Control microscale fluids	Study interstitial flow effects	
Suppressing Tumor Epigenetic Modifications	Adjusting ECM Stiffness and Solid Stress	Reduce ECM hardness and fibrosis	Affect epigenetic modifications in tumor cells	145–148
		Use enzymes for ECM degradation	Prevent ECM crosslinking and modify stromal cell activity	
	Targeting Mechanical Sensing Pathways with Drugs	Inhibit sensors/pathways	Disrupt mechanical sensing and epigenetic responses	149–153
		FAK, TAZ, YAP inhibitors	Target mechanical sensors/pathways	
	Physical Intervention Therapy	TTFields	Impede cancer cell division	155–158
		HIFU	Destroy tissue or enhance drug delivery	

4. Biomechanical characteristics could potentially serve as biomarkers for epigenetic changes, as well as for assessing tumor progression and treatment efficacy. The advent of biomechanical tools allows researchers to clearly detect the interactions between cellular mechanical forces and epigenetic changes, providing a window to understand the effects of mechanical forces on cells and molecules. It has identified mechanical properties as potential biomarkers for tumor epigenetics. And facilitate non-invasive monitoring of epigenetic dynamics in tumor tissues before and after treatment. Furthermore, the refinement and application of cutting-edge models and imaging techniques that allow for in vivo observation of mechanical properties in tissues and cells could yield real-time insights.
5. In terms of therapeutic potential, manipulating mechanical factors such as the stiffness of the extracellular matrix or targeting mechanosensing pathways pharmaceutically may help to curb tumor epigenetic changes. This opens new avenues for cancer therapy. Additionally, given the heterogeneity of tumors, it is anticipated that personalized biomechanics-based interventions, attuned to the unique biomechanical and epigenetic landscape of each tumor, could inform clinical treatments.

Merging biomechanics with tumor epigenetics necessitates interdisciplinary approaches. Bolstering collaboration among biologists, clinicians, and pharmacologists is vital to harness the full potential of this cross-disciplinary field. In conclusion, integrating biomechanics into tumor epigenetics research not only deepens our comprehension of cancer biology but also introduces a plethora of new treatment possibilities.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

CRediT authorship contribution statement

Qi Wang: Conceptualization, Writing – original draft. **Xiaohong Yin:** Conceptualization, Writing – original draft. **Yunyi Ding:** Conceptualization, Formal analysis. **Hong Zhao:** Conceptualization, Formal analysis, Supervision. **Yichen Luo:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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