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Review

Mechanobiology research in China

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ABSTRACT

Mechanobiology is an interdisciplinary discipline combining biology, engineering, chemistry, physics, and medicine. Mechanobiology research comprehensively discusses, the role of mechanical factors in various life processes and the occurrence and development of associated and diseases at the whole organism, organ, cell, protein and gene levels. The cellular and molecular mechanisms of mechanical signal transduction and response are elucidated, in addition to the discovery of novel biomarkers and potential drug targets, which are mechanosensitive molecules. This paper reviews the development of mechanobiology research in China since the new century, while focusing on the research achievements of Chinese scientists in the field of mechanobiology over the last three years, including cardiovascular, bone and joint, tumor, cellular, and molecular mechanobiology. Meanwhile, it has been suggested that in the future, mechanobiology research should include are indicated detailed studies on the mechanobiological mechanism of diseases at the cellular and molecular levels firstly, so that the newly discovered biomarkers or potential targets can gradually achieve clinical transformation. Second, future research should strengthen the qualitative and quantitative combination of biological experiments and mechanical and mathematical modeling analyses, especially at cellular, subcellular and molecular scales. Mechanobiological studies are of great theoretical and practical significance for our understanding of the mechanical mechanisms and natural laws of growth and senility of the human body, expounding pathological mechanisms of diseases, and researching and developing new medicines and technologies to promote biomedical and clinical research for human health.

Mechanobiology is a new and important field of study in biomechanics. It studies the effects of the internal and external mechanical environment on health, disease, or injury; mechanosensitive responses and their mechanisms; and inter-relations between mechanical and biological processes, such as growth, adaption, remodeling, and repair [1,2]. Through the organic combination of biological and mechanical principles and methods, the role of mechanical factors in the occurrence and development of life processes and diseases is comprehensively discussed at the whole, organ, cell, protein, and gene levels. The cellular and molecular mechanisms of mechanical signal transduction and response are elucidated, along with the discovery of new biomarkers and potential drug targets, which are mechanosensitive molecules. These studies are of great theoretical and practical significance for our understanding of the mechanical mechanisms and natural laws of growth and senility of the human body, expounding pathological mechanisms of diseases, and researching and developing new medicines and technologies to promote the development of basic biomedical and clinical research for human health. Mechanobiological concept has also significantly influenced various fields such as biology, biomaterials, tissue engineering, chemistry, and micro/nano processing technology.

Biomechanics studies the deformation and movement of living entities to recognize the laws of life processes and solve scientific issues in the field of life and health. Y. C. Fung, the father of biomechanics, proposed the stress-growth law in his monograph, '*Biomechanics: Motion, Flow, Stress, and Growth*', 1990, which states that remodeling of blood vessels involving growth or resorption of cell and extracellular materials is linked to stress in the vessel [3]. The stress-growth law is a fundamental theory that expounds the intrinsic relationship between the most basic form of matter movement, mechanical motion, and the highest form, life motion, and guides the transformation of biomechanics from mechanics applied to biology to the organic bond of mechanics with biological processes. Qualitative changes and the development of biomechanics are observed. Mechanobiology, as a new frontier field of biomechanics, has developed in response to advances in cell and molecular biology techniques.

In 1998, the first session on mechanobiology was held at the 3rd World Congress on Biomechanics (WCB). Since then, mechanobiology, as

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a new frontier interdisciplinary field, has received increasing attention from international scientists, and research in this field is in ascendance worldwide. At the same time, mechanobiology research has been conducted in China.

In 2003, the first mechanobiology laboratory in China was established at Shanghai Jiao Tong University (SJTU). In 2005, the 57th Eastern Science and Technology Forum was held in Shanghai with the themes of mechanobiology and medical engineering, which was organized by the Shanghai municipal government, the Chinese Academy of Sciences and the Chinese Academy of Engineering. Since then, the National Conference on Biomechanics and other related academic conferences in China have also set up mechanobiology sessions. In 2008, the Advanced Workshop in Biomechanics funded by the National Natural Science Foundation of China (NSFC) was held at SJTU.

In 2009, the Seminar on Advanced Issues in Cardiovascular Mechanobiology was hosted by the China Association for Science and Technology. In the summer of 2016, the Advanced Workshop on Mechanobiology, funded by the NSFC, was held at SJTU. A total of 270 scholars from more than 60 universities and institutes in China attended the workshop, and more than 30 professors from China and the USA gave lectures. These academic activities have vigorously promoted the development of mechanobiology research in China.

After more than ten years of development, mechanobiology research in cardiovascular, bone and joint, stem cell, tumor, stomatology and other fields has been conducted in China. Using proteomic techniques, two-dimensional electrophoresis, and mass spectrometry, the protein profiles of the aortas of SD rats [4] and spontaneously hypertensive rats [5] cultured under two levels of shear stress were determined by the SJTU team. Based on vascular proteomic analysis, a vascular cell mechanotransduction network has been established using a systemic biological approach encompassing high-throughput screening, bioinformatics analysis, and biological validation [6]. Then, the roles of PDGF-BB and TGF-β1 on cross-talk between endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) in vascular remodeling induced by low shear stress, and the roles of nuclear envelope proteins in the proliferation of VSMCs subjected to cyclic stretch [6,7], and the proliferation and apoptosis of ECs in response to shear stress [8] were evaluated respectively. The Chinese University of Hong Kong, Tianjin Medical University and other teams collaborated to report that the integrin-YAP/TAZ-JNK cascade mediates the atheroprotective effect of unidirectional shear flow [9]. The Tsinghua University teams reported the mechanism of induction of stem cell differentiation by extracellular matrix (ECM) elasticity [10], and the mechanotransduction mechanism of mechanosensitive Piezo channels [11,12].

In 2017, the '*Frontiers on Biomechanical Research Series*', a set of ten volumes, was published by SJTU Press, including two monographs on '*Vascular Mechanobiology*' [13] and '*Mechanobiology in Stomatology*' [14]. This series summarizes the achievements of biomechanical research in China since the new century. Prof. Y. C. Fung wrote an inscription for the series, '*To Develop Biomechanics for the Benefit of Human Health*'. Prof. Shu Chien wrote the forewords for this series [13,14]. The publication of this series became a milestone in the development of biomechanical research in China and laid a solid foundation for future research in biomechanics.

Since 2020, the COVID-19 pandemic has devastated the world and has had a significant impact on all aspects of humanity. Chinese researchers have overcome many difficulties and have made great achievements in their research. The following is a brief introduction to the progress made by Chinese scientists in the field of mechanobiology in the last three years.

1. Cardiovascular mechanobiology

Cardiovascular disease is one of the most serious health hazards. Elucidation of the pathogenesis of cardiovascular disease for its prevention is a major field of biomedical and mechanobiological research [15,16]. Cardiovascular disorders, including hypertension, atherosclerosis, and stroke, are essentially vascular diseases. They have a common pathogenic mechanism and basic pathological process, *i.e.*, vascular remodeling, which includes cardiovascular cell migration, hypertrophy, proliferation and apoptosis, as well as changes in cell phenotype, morphological structure and function [16]. The cardiovascular system can be considered a mechanical system in which the heart occupies the central position and functions as a mechanical pump. Blood circulation involves the flow of blood, deformation of blood cells and blood vessels, and interaction between the blood and vessels, which comprise several mechanical mechanisms. Many clinical and experimental studies have demonstrated that biological, chemical, physical, and other factors affect vascular remodeling *in vivo* and *in vitro*, in which mechanical factors play a direct and important role [16]. Cardiovascular mechanobiology elucidates how mechanical factors induce biological effects that result in vascular remodeling. It allows for a understanding of the mechanical basis of blood circulation and the natural laws of growth, development, and senility of the vasculature and expounds the pathological mechanism of cardiovascular diseases at the cellular and molecular levels.

Coronary artery disease is one of the most prevalent cardiovascular disorders. Vein-graft-based coronary artery bypass surgery is an effective therapeutic approach. However, vein graft stenosis occurs after coronary artery bypass grafting, which is a major cause of vein graft failure [17,18]. Vein grafts exposed to arterial circulation exhibit rapid endothelial damage during the early stage [19]. Endothelial injury contributes to neointima formation and vein graft failure [20] by activating abnormal migration and proliferation of VSMCs [21].

VSMCs in a vascular medium are subjected to cyclic circumferential strain, that is cyclic stretching. Once a vein graft is transplanted into the arterial system, such as the saphenous vein in a coronary artery bypass graft, the transplanted vessels are exposed to the arterial mechanical environment. The arterialized cyclic stretch affects VSMC functions in grafted veins, including excessive proliferation and migration which causes neointima formation and ultimately leads to vein graft failure. Huang et al. established a graft vein rat model and observed that neointimal hyperplasia and cell proliferation were significantly increased and miR-33 expression was decreased at 1-, 2-, and 4-week post grafting. Venous VSMCs were exposed to mimic arterial cyclic stretch using a cell stretch loading system *in vitro* to explore the mechanism at the cellular molecular level [22]. They reported a novel mechanism through which microRNA-33 (miR-33) mediates mechanical stretch-induced VSMC proliferation and neointimal hyperplasia. Thus, miR-33 targeting may be a novel therapeutic strategy to prevent vein graft failure and neointimal hyperplasia [22]. Although previous studies demonstrated that miR-33 affects vein graft-induced neointimal hyperplasia, several important questions remain unanswered, including the molecular mechanism and mechanosensors that control miR-33 expression in response to arterial stretch of VSMCs and vascular injury. Whether miR-33 is involved in human vein graft adaptation is an interesting research topic. The mechanism of action of miRNAs in mechanotransduction has not yet been fully elucidated. Specifically, miRNAs can regulate multiple target genes in the cell signaling network, greatly influencing biological pathways, cell functions and the dynamic balance of the vessel wall. miRNAs as biomarkers or therapeutic targets may be superior to existing biomarkers or treatment drugs for cardiovascular diseases. Recently, Liu et al. reported the role of Lamtor1 in neointimal formation and the regulatory mechanism of non-coding RNA underlying the process of vein graft-induced neointimal hyperplasia [23]. Using VSMC-specific Lamtor1 KO mice, the venous graft model was replicated, and venous VSMCs were exposed to mimic arterial cyclic stretch using a cell stretch loading system *in vitro*. Their results showed that Lamtor1 was significantly enhanced in grafted veins and activated mTORC1 signaling to promote the dedifferentiation of VSMCs *in vivo*. Arterial mechanical stretch induced circSlc8a1 expression, positively regulated Lamtor1, activated mTORC1, and promoted VSMC dedifferentiation and proliferation. Local injection of circSlc8a1 siRNA or VSMC-specific Lamtor1 knockout mice prevented neointimal hyperplasia in vein grafts *in vivo* (Fig. 1) [23]. This study

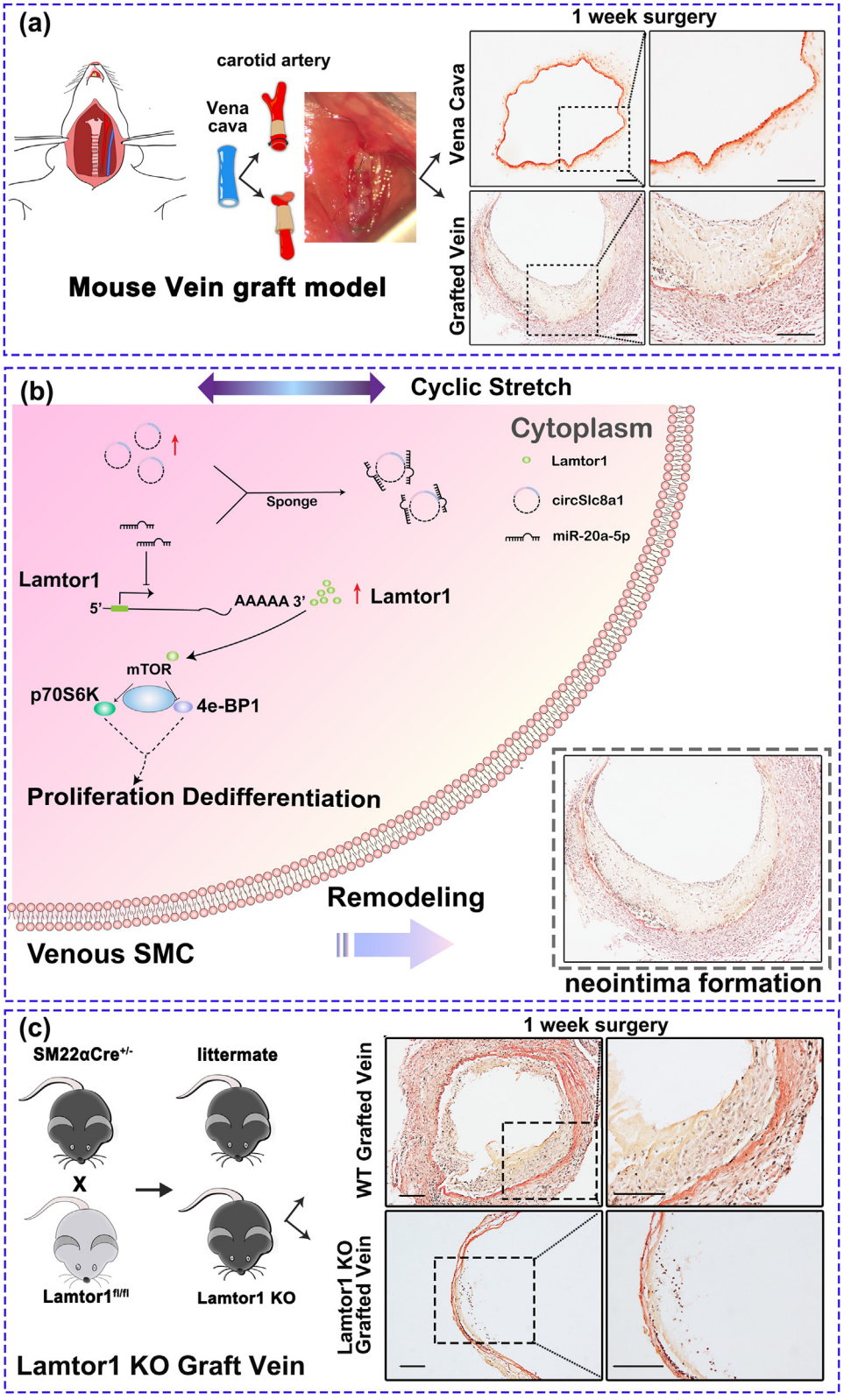

Fig. 1. A schematic diagram of the mechanobiological mechanism of circSlc8a1 in vein graft remodeling. (a) Schematic depiction of vein graft using the nonsuture cuff technique anastomosing recipient common carotid artery with the donor inferior vena cava in rat. The vein grafting increases the expression of Lamtor1 and induces neointimal hyperplasia. (b) Schematic drawing of the mechanisms of Lamtor1 in intimal hyperplasia after graft surgery. Arterial cyclic stretch induces the expression of circSlc8a1 which subsequently increases Lamtor1 expression and the proliferation and dedifferentiation of venous SMCs. (c) SM-specific Lamtor1 KO mice was generated by Cre-LoxP system and representative images of Elastin-van Gieson staining revealed that neointimal formation was significantly reduced in SM-specific Lamtor1 KO mice.

revealed a novel mechanobiological mechanism underlying the dedifferentiation and proliferation of VSMCs in neointimal hyperplasia. The CircSlc81/miR-20a-5p/Lamtor1 axis induced by arterial cyclic stretch may be a potential target for attenuating neointimal hyperplasia in grafted vessels.

Another novel regulatory mechanism underlying the process of vein graft-induced neointimal hyperplasia suggested that mitochondrial protein MFN2 (mitofusin2) is a mechanoresponsive protein that interacts with PFK1 (phosphofructokinase1) to mediate the ubiquitin-protease-dependent PFK1 degradation and therefore suppresses glycolysis in VSMCs [24]. These findings suggest that targeting the transition of OXPHOS (oxidative phosphorylation) to glycolysis and the MFN2-PFK1 axis are potential interventions for preventing neointimal formation. These studies demonstrated that miR-33,

CircSlc81/miR-20a-5p/Lamtor1 axis, and MFN2-PFK1 axis affect vein graft-induced neointimal hyperplasia. Further studies should be conducted to translate these potential targets into the prevention and treatment of neointimal hyperplasia in clinical practice.

The focal nature of atherosclerosis suggests a critical role of local hemodynamic microenvironments in atherogenesis [15,16,19]. Disturbed flow with low and reciprocating shear stress (oscillatory shear, OS) in arterial branches and curvatures up-regulates proinflammatory molecules in ECs, thereby inducing the filtration of circulating monocytes into the arterial wall and VSMC migration into the subintimal space, leading to atherosclerosis [25,26]. In contrast, laminar flow with high unidirectional shear stress (pulsatile shear, PS) in the straight parts of the arteries elicits an mechanosensory and atheroprotective effect on the vasculature [25,26]. Distinct gene expression patterns and phenotypes in ECs provoked by disturbed *vs.* laminar flows develop before the appearance of any functional outcomes, and they have been suggested as hallmarks of an atherosusceptible or atheroresistant endothelium.

The importance of endothelial gene expression and phenotype in atherogenesis has been recognized. A systematic understanding of the functional connections among the atherogenic phenotypes of the endothelium, gene expression, and drug actions can lead to effective anti-atherosclerotic drug screening. Zhao et al. reported that apurinic/apyrimidinic endonuclease1 (APEX1) is a shear stress-sensitive molecule that plays a crucial role in atherogenic flow-induced endothelial proinflammatory responses. Depletion of endothelial Apex1 in mice ameliorates atherogenesis [27]. They demonstrated that vitexin, a natural flavonoid, can inhibit the activation of APEX1 to protect the vascular endothelium against the adverse effects of atherogenic stimuli [27]. These findings suggest that targeting APEX1 with vitexin represents a potential therapeutic strategy for the treatment of endothelial inflammation and related diseases.

In addition to the above reports, Chinese scholars have made many new advances in the mechanobiological mechanisms of atherosclerosis and cardiovascular diseases. Shih et al. reported that vinculin phosphorylation impairs vascular endothelial junctions to promote atherosclerosis and indicated that endothelial phosphorylation at serine 721 (VCLS721p) is a valuable hemodynamic-based target for the clinical assessment and treatment of vascular disorders resulting from atherosclerosis [28]. Wei et al. confirmed that disturbed flow induces endothelial phospho-YY1^{S118} (serine [S]118 phosphorylation of Yin Yang 1) to promote atherosclerosis, indicating that phospo-YY1^{S118} is a potential target for atherosclerosis [29]. Vascular calcification in the arterial intima is closely associated with atherosclerosis, which occurs in branched or bifurcated areas of the vasculature. Laminar flow inhibits vascular calcification through KLF2 (Krüppel-like factor 2) -mediated inhibition of endothelial BMP/SMAD1/5 signaling. Targeting KLF2 may represent a novel therapeutic approach against vascular calcification [30]. KLF2 mediates fluid shear stress-dependent regulation of UCP2 (uncoupling protein 2) expression in ECs. UCP2, a key mitochondrial antioxidant protein, is critical for endothelial proinflammatory response and atherogenesis [31]. The translocation of integrin α5 to lipid rafts promotes integrin activation and ligation, which is critical for OS-induced EC activation. Zhang et al. elucidated a novel endothelial mechanotransduction molecular mechanism linking atheroprone flow and integrin α5β1 activation, thereby identifying a class of potential therapeutic targets for atherosclerosis [32]. MST1 (mammalian sterile 20-like kinase 1), the primary kinase in the mechanosensitive Hippo pathway, disturbed flow-induced EC activation and atherosclerosis. Inhibition of the MST1-Cx43 (connexin 43) axis is an essential driver of OS-induced endothelial dysfunction and atherosclerosis [33]. Kong et al. found that an atherogenic high-cholesterol diet diminished the endothelial glycocalyx and disturbed the local nitric oxide (NO) release, thus contributing to the impaired vasomotor properties of the vessel [34]. They also suggested that the endothelial glycocalyx may also act as a mechanosensor of shear to regulate EC apoptosis, thus affecting leaky junctions and regulating low density lipoprotein (LDL) transport [35].

GTPase-activating SH3 domain-binding protein 2 (G3BP2) is a mediator that responds to environmental stress through stress granule formation and is involved in the progression of chronic diseases. Low oscillatory flow as a strong stimulation of ECs can up-regulate the aggregation of G3BP2 and form a phase separation structure, leading to EC dysfunction and atherosclerosis through inflammation [36,37]. It was also confirmed that low oscillatory flow inhibited the expression of demethylase truncated TET1s, resulting in histone acetylation changes that increased EC cell permeability and caused atherosclerosis [38]. As a mediator of ECM protein degradation, cathepsin K (CTSK) was directly regulated by hemodynamics and contributed to atherosclerosis [39]. Therefore, a novel CTSK-responsive targeted nanodelivery system was designed to significantly reduce lipid deposition in the aorta and inhibit plaque development [40], providing a new approach for clinical atherosclerosis-targeted drug delivery therapy.

ECs *in vivo* are subjected to three forms of shear stress simultaneously induced by luminal blood flow, transendothelial flow and interstitial flow. It is controversial whether shear stress, especially the component induced by luminal flow, inhibits the initialization of angiogenesis and triggers arteriogenesis. Zhao and Liu et al. combined microfabrication techniques and delicate numerical simulations to reconstruct a three-dimensional vascular chip and its control system *in vitro* to simulate the vascular microenvironment, where ECs experience high luminal shear stress, physiological transendothelial flow and various vascular endothelial growth factor (VEGF) distributions simultaneously [41]. The results showed that distraction from the stabilized state, such as decreased luminal shear stress, increased VEGF, and the destruction of mechanotransduction of heparan sulfate proteoglycan (HSPGs) induces the initiation of neovascularization [41]. Their study provided a novel approach for vascular mechanobiological studies and highlighted the key role of the magnitude and forms of shear stress in neovascularization.

2. Bone and joint mechanobiology

Bones and joints are the main parts of the locomotion system, which are responsible for supporting, moving, load-bearing and protecting internal organs. Osteoarthropathy is a common clinical disease and an the important field in mechanobiology research. As Wolff's law states, bone architecture reshapes in response to mechanical force throughout the life span. Bone constantly responds and adapts to changes in mechanical loads associated with body weight, movement and gravity. Proper loading stimuli from daily movements, such as gravity or optimal intensity of exercise, maintain bone mass and strength and thus prevent bone loss. Furthermore, owing to their noninvasive nature and convenience, mechanical therapies, including shockwaves, orthodontics, distraction osteogenesis, and surgical tension reduction, have emerged as a common choice for osteoarthropathy and other defects [42]. These mechanical forces play a crucial role in maintaining skeletal integrity, including bone quality and quantity. The mechanical load-induced bone remodeling process is determined by the functional interaction between bone-forming osteoblasts and bone-absorbing osteoclasts. Dysfunctions in mechanotransduction signaling can disrupt bone remodeling and induce an imbalance in bone homeostasis, leading to abnormal changes in bone mass and disorganized bone architecture [43,44]. Therefore, the study of the mechanobiological mechanism of bone remodeling is helpful for understanding the law of bone growth, development and aging, and provides a mechanobiological basis for revealing the occurrence, development mechanism and prevention of osteoarthropathy.

To detect and respond to mechanical forces, cells use specialized sensor proteins. One of the mechanosensitive proteins, i.e. Piezo, is found on the surface of many different types of cells, and helps cells respond to touch, pressure, or stretching of the surrounding tissue [45–48]. Wang et al. reported that the mechano-forced-sensitive channel protein Piezo1 regulates the extracellular matrix in osteoblasts through YAP, thereby inhibiting osteoclast formation and maintaining bone remodeling homeostasis [49]. This provides a new idea to understand how mechanical

stress regulates the balance between bone formation and bone resorption and a potential strategy for the treatment of disuse osteoporosis.

Osteoarthritis (OA) is one of the most common joint degenerative diseases and has the clinical manifestations of joint pain, abnormal function and joint deformity, as well as causing serious physical and mental pressure and a huge economic burden. Currently, the treatment of OA is limited to symptom relief and joint replacement in the advanced stages, and there are no effective treatment strategies to alleviate the progression of the disease. As a load-bearing structure closely related to body activities, articular cartilage is constantly stimulated by various forces, such as shear stress, tensile stress and pressure. Abnormal force stimulation can damage the cartilage tissue, leading to apoptosis, extracellular matrix degradation and cartilage degeneration. However, the role and mechanism of abnormal force stimulation in inducing osteoarthritis remain unclear.

Jin et al. confirmed the upregulation of the histone demethylase JMJD3 (Jumanji domain-containing protein D3) in aberrant force-induced cartilage injury *in vitro* and *in vivo*. Functionally, inhibition of JMJD3 by its inhibitor, GSK-J4, or downregulation of JMJD3 by adenovirus infection of sh-JMJD3 could alleviate aberrant force-induced chondrocyte injury. Mechanistic investigation illustrated that aberrant force induces JMJD3 expression and demethylates H3K27me3 at the NR4A1 promoter to upregulate its expression. Further experiments indicated that NR4A1 could regulate chondrocyte apoptosis, cartilage degeneration, extracellular matrix degradation, and inflammatory responses. *In vivo*, anterior cruciate ligament transection (ACLT) was performed to construct an OA model, and the therapeutic effect of GSK-J4 was validated. More importantly, a peptide-siRNA nanoplatform was adopted to deliver si-JMJD3 into the articular cartilage, and the severity of joint degeneration was remarkably mitigated (Fig. 2). These findings demonstrate that JMJD3 is force-responsive and epigenetically regulates OA progression [50]. This study revealed the important role of epigenetic regulation in OA induced by abnormal forces, clarified the key mechanism of the signaling axis of FSS-JMJD3-H3K27me3-NR4A1-Akt in promoting the occurrence and development of OA, and provided new mechanobiological approaches for potential targeted treatment strategies for OA.

Recently, it has been found that mitochondria, acting as critical mechanotransducers, are at the intersection of extracellular mechanical signals and chondrocyte biology, and mechanical loading-induced mitochondrial dysfunction contributes to the pathogenesis of osteoarthritis [51]. The variation in tibial plateau subchondral trabecular bone (STB) remodeling activity and microstructure has been associated with knee alignment [hip-knee-ankle (HKA) angle] and cartilage degradation. Knee malalignment may cause abnormal STB remodeling and microstructural sclerosis, which may potentially affect load stress transmission from the cartilage to the STB, resulting in accelerated knee OA progression [52]. Mechanical overload and chondrocyte senescence play essential roles in OA development. F-box and WD repeat domain containing 7 (FBXW7), a ubiquitin ligase, are key factors in the association between mechanical stress and chondrocyte senescence in OA. Zhang et al. reported that excessive mechanical loading downregulates FBXW7 to activate MKK7–JNK signaling, which stimulates chondrocyte senescence and consequently initiates and accelerates OA development, whereas inhibition of JNK activity ameliorates chondrocyte senescence and cartilage degeneration [53]. They demonstrated that FBXW7 is a key factor in the association between mechanical overloading and chondrocyte senescence and cartilage aging in the pathology of OA and suggested that targeting FBXW7-MKK7-JNK signaling may be a novel therapeutic approach for OA treatment [53].

3. Tumor mechanobiology

Malignant tumors seriously affect human life and health. The mechanisms of occurrence, progression, invasion, and metastasis of cancer and its prevention and treatment are scientific and social issues that have attracted close attention worldwide. The mechanical and chemical microenvironments strongly influence the occurrence, progression, invasion, and metastasis of tumor cells. Therefore, this field is also a high focus of mechanobiological research.

Biomechanical and biochemical cues constitute the dynamic and heterogeneous tumor microenvironment (TME), which is mainly composed of three parts: cellular components (stromal cells, fibroblasts, immune cells, pericytes, etc.), ECM, and vasculature (blood vessels and

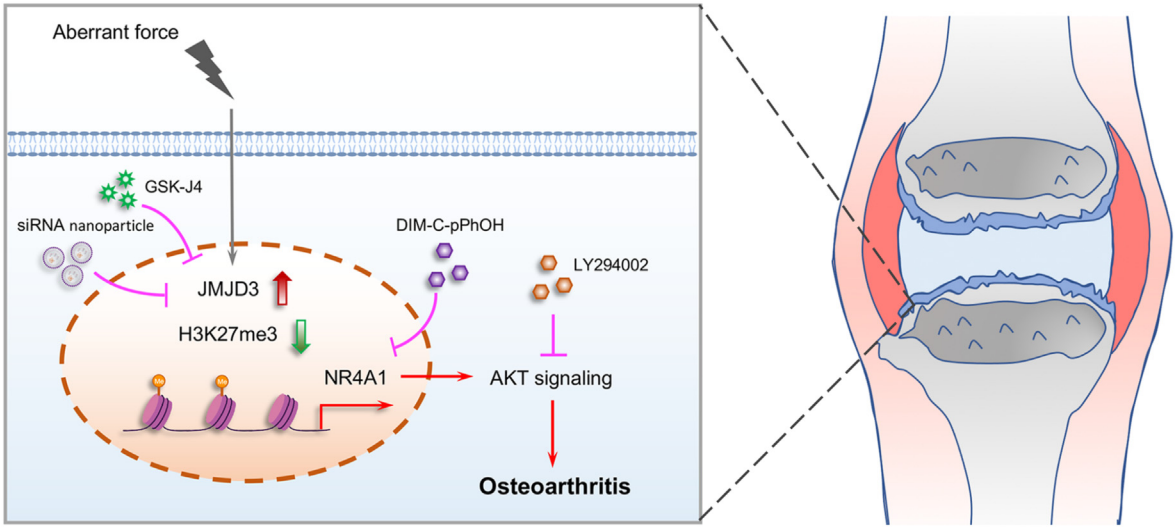

Fig. 2. A schematic view illustrating the epigenetic regulatory mechanism of JMJD3 in aberrant mechanical force-related OA. The upregulation of JMJD3 in aberrant force-induced cartilage injury *in vitro* and *in vivo* were confirmed. The inhibition of JMJD3 by its inhibitor, GSK-J4, or downregulation of JMJD3 by adenovirus infection of sh-JMJD3 could alleviate the aberrant force-induced chondrocyte injury. The aberrant force induces JMJD3 expression and then demethylates H3K27me3 at the NR4A1 promoter to promote its expression. NR4A1 can regulate chondrocyte apoptosis, cartilage degeneration, extracellular matrix degradation, and inflammatory responses. *In vivo*, anterior cruciate ligament transection (ACLT) was performed to construct an OA model, and the therapeutic effect of GSK-J4 was validated. A peptide-siRNA nanoplatform was adopted to deliver si-JMJD3 into articular cartilage, and the severity of joint degeneration was remarkably mitigated. It revealed that the important role of epigenetic regulation in OA induced by abnormal forces, and the key mechanism of the signaling axis of force-JMJD3-H3K27me3-NR4A1-Akt in promoting the occurrence and development of OA (From Jin et al. Ref. [50]).

lymphatic vessels). The TME provides physical support for tumor cells to adhere and absorb nutrients, and escape from the immune system, which facilitates the emergence and development of tumors (Fig. 3) [54]. Dynamic and heterogeneous interactions between tumor cells and the surrounding microenvironment fuel the occurrence, progression, invasion, and metastasis of solid tumors. Tumor cells sense and respond to the strength, direction, and duration of mechanical cues in the TME via various mechanotransduction pathways. Owing to significant therapeutic difficulties caused by the mechanical changes in TME, emerging studies have focused on targeting the adverse mechanical factors in TME to attenuate disease rather than conventionally targeting tumor cells themselves, which has been proven to be a potential therapeutic approach and has become a major topic in the study of tumor mechanobiology. Zhou et al. systematically discussed the origins and roles of mechanical factors in TME, cell sensing, mechano-biological coupling and signal transduction, *in vitro* construction of the tumor mechanical microenvironment, and applications and clinical significance in TME [54].

The TME is characterized not only in terms of chemical composition, but also by physical properties such as stiffness, which influences the morphology, proliferation, and fate of tumor cells. Chen et al. cultured human breast cancer MDA-MB-231 cells on rigid (57 kPa), stiff (38 kPa) or soft (10 kPa) substrates and demonstrated that increasing autophagy levels and autophagic flux in cells cultured on soft substrates partly attenuated soft substrate-induced apoptosis. Mechanistically, this protective autophagy is regulated by intracellular reactive oxygen species (ROS) accumulation, which triggers downstream signals of JNK, Bcl-2, and Beclin-1. More importantly, soft substrate-induced activation of ROS/JNK signaling promotes cell apoptosis through the mitochondrial pathway, whereas it increases protective autophagy by suppressing the interaction between Bcl-2 and Beclin-1 [55]. These data suggest that JNK is a mediator of soft substrate-induced breast cancer cell apoptosis and autophagy which is likely to be the mechanism that partly attenuates mitochondrial apoptosis. This study provides new insights into the molecular mechanisms by which autophagy plays a protective role against soft substrate-induced apoptosis in human breast cancer cells. Stiffening of the ECM during tumor progression results in increased cancer cell motility. During cell migration, two major isoforms of non-muscle myosin II (NMII), NMIIA and NMIIB, are expressed and assembled into the cytoskeleton. However, the isoform-specific regulatory roles of NMIIA and NMIIB as well as the underlying mechanisms in response to mechanical cues of the ECM remain elusive. Based on polyacrylamide (PAA) gels with tunable elastic moduli, Peng et al. mimicked the mechanical properties of tumor tissue at different stages of breast cancer *in vitro* and investigated the distinct roles of NMII isoforms in the regulation of substrate stiffness [56]. They demonstrated that NMIIA is engaged in establishing cell polarity by facilitating lamellipodia formation, focal adhesion turnover, and actin polymerization at the cell leading edge,

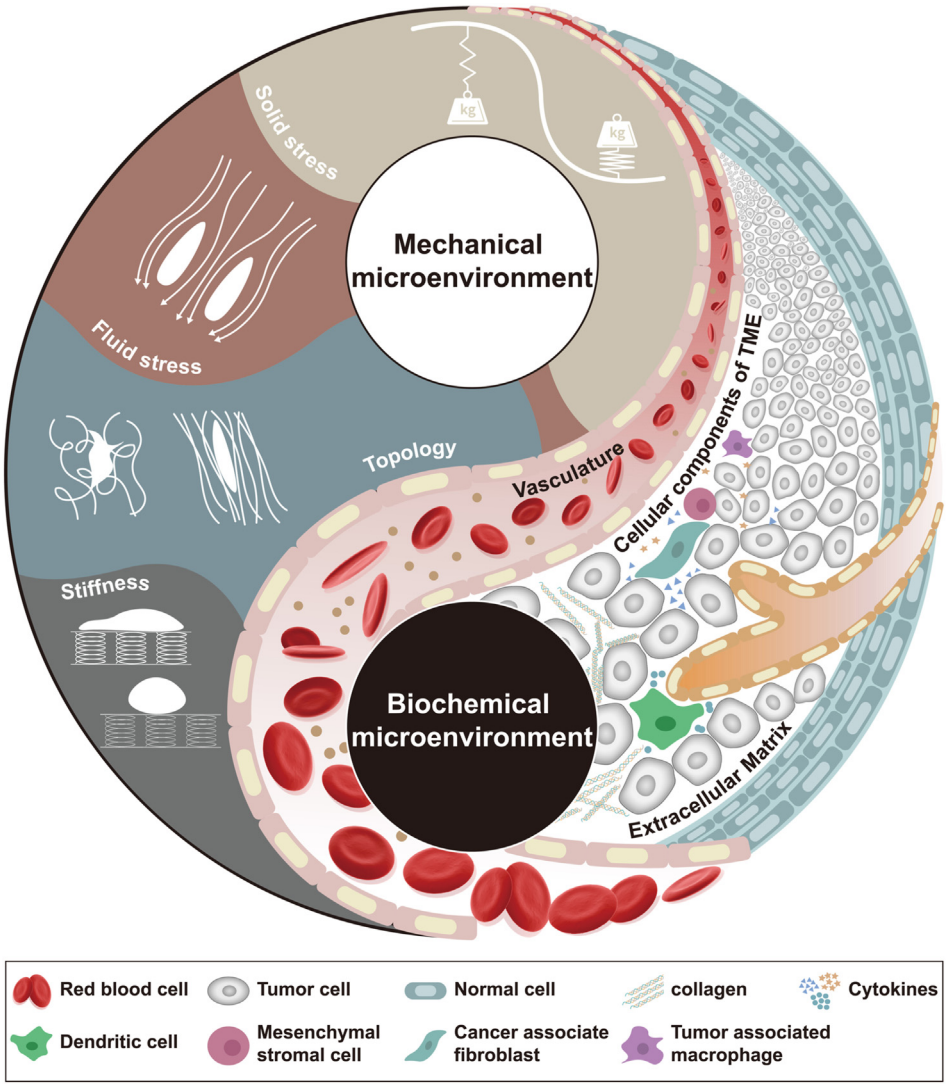

Fig. 3. Properties of tumor microenvironment (TME). As a comprehensive environment, TME is mainly divided into two parts: (i) the biochemical microenvironment and (ii) the mechanical microenvironment. Due to the changes in biochemical components in TME, the physical properties are dramatically changed. Uncontrolled proliferation of tumor cells constantly compresses adjacent tissues and tumor vasculature, generating internal high-pressure solid stress and further resulting in increased blood/interstitial pressure. The imbalance between pro- and anti-angiogenic factors causes abnormal tumor vasculature that generates much pressure on TME. Alterations in the composition and density of the extracellular matrix (ECM) occur frequently in tumors. Cancer-associated fibroblasts (CAFs) are constantly remodeling (by depositing or cross-linking) ECM to cope with mechanical stress in TME, leading to increased stiffness and altered topology. Stiffness (rigidity) refers to the resistance to deformation in response to applied force, which is measured as Young's elastic modulus. Topology (architecture) comprises ECM porosity, fibril orientation and other fibril characteristics, which wield important influences on cell polarity and function. The subtle and mutualistic relationship between tumor cells and their TME properties is formed early in solid tumor growth and evolves throughout the complete life cycle. (From Zhou et al. [54]).

whereas NMIIB is recruited to the cell perinuclear region and contributes to traction force generation and polarized distribution, both in a substrate stiffness-dependent manner. They further validated that substrate stiffness modulates the distribution and activation of NMII isoforms via the Rac1/p-PAK1/pS1916-NMIIA and PKCζ/pS1935-NMIIB signaling pathways in a site- and kinase-specific phosphoregulation manner [56]. This study allowed for an understanding of the mechanotransduction of cancer cells and provides inspiration for molecular targets in anti-metastatic therapy. The survival of cancer stem cells is usually limited to a specific TME, which plays a vital role in tumor development. The mechanical properties of the TME differ in different regions of solid tumors. Sun et al. constructed a rat liver pathological model demonstrating sequential progression from hepatitis to liver fibrosis/sclerosis culminating in liver cancer, and analyzed the mechanical properties of liver tissues during the pathological process. Liver cancer tissues showed significant mechanical heterogeneity, and the distribution of liver cancer stem cells (LCSCs) in liver cancer tissues was significantly correlated with the mechanical heterogeneity of liver cancer tissues [57]. They also used an oxidized sodium alginate hydrogel to establish a three-dimensional cell culture system and studied the effects of substrates of different stiffness on the stemness of LCSCs. It was confirmed that the stemness of LCSCs could respond to changes in the stiffness of substrates through the force-sensitive molecule YAP [58]. Based on the mechanical properties of the ECM of liver cancer tissue, Chen et al. constructed a ZIF-90 nano-drug delivery system, modified with osmopeptide and simultaneously embedded anti-cancer drug adriamycin and Notch signaling pathway inhibitor of tumor stem cells, and confirmed that the nano-drug could effectively penetrate the liver tumor tissue and kill liver cancer cells and tumor stem cells, thus improving the antitumor effect [59].

It is becoming increasingly clear that the motion of nucleated cells in the blood-stream is essential for illuminating the role of hemodynamics in the mechanobiological response of cells. For example, circulating tumor cells (CTCs) that are shed from the primary tumor and invade the circulatory system are key mediators of cancer metastasis. Membrane tensions of CTCs arising from viscous shear and elastic compression in microvessels are important mechanical stimulations that trigger downstream signaling pathways, promote adhesion and extravasation, induce tumor cell apoptosis or autophagy, and regulating the proliferation of tumor cells [60]. CTCs are known to spread quickly and invasively through bloodstream, but few studies have quantified the stress associated with their motion in the blood. Jing et al. developed a numerical method to understand the biomechanics of circulating tumor cells more accurately in blood vessels of varying sizes [60]. They found that in narrower blood vessels, tumor cells of larger or comparable size are the primary reason why the membranes experience tension, or force along the entire membrane. However, in larger blood vessels, red blood cells can concentrate tumor cells along the vessel walls, leading to localized, increased tension along the inside perimeter of the vessels [60]. Although the margination effect is expected to be enhanced with higher hematocrit in large vessels, the present work clarifies that the increase in hematocrit promotes membrane tension not only by increasing the local shear rate with the margination, but also by limiting the relaxation of the membrane tension by suppressing CTCs rotational motion. To numerically simulate tumor cells circulating in blood vessels, the team used the immersed boundary method, which considers both the motion and deformation of cells. They further set up simulations to examine, among other parameters, the deviatoric tensions, principal tension, and average isotropic tensions of CTCs in the membrane as references for the mechanobiological study of cancer cell mechanics [60]. For future studies, we plan to use a more realistic cell model that considers more details about the structures and properties of cells and membranes.

CTCs acquire enhanced anti-anoikis abilities after experiencing flow-shear stress in the circulatory system. Reactive oxygen species (ROS) and nitric oxide (NO) are classic reactive species in redox signaling that are related to homeostatic maintenance and promote various physiological and pathological processes. Low shear stress (LSS) promotes anoikis resistance in human breast carcinoma cells via caveolin-1 (Cav-1)-dependent extrinsic and intrinsic apoptotic pathways [61]. After tumor cells escape from the ECM, invade through the basement membrane, and enter the circulation system, the expression of the classic reactive species ROS and NO is upregulated by shear stress. Along with the accumulation of ROS and NO, proteolysis via the ubiquitin-proteasome pathway is gradually inhibited. Enhanced stabilization and expression of Cav-1 prevents mitochondrial membrane permeabilization by downregulating of the Bax/Bcl-2 ratio, reducing the activation of caspase-3, and subsequently inhibiting the apoptosis signaling pathway [62].

4. Cellular and molecular mechanobiology

The above-mentioned studies on cardiovascular, bone and joint, and tumor mechanobiology have been conducted both *in vivo* and *in vitro* according to disease classification, revealing the cellular and molecular mechanisms of the occurrence and progression of diseases. Although mechanobiology research is bound to involve the research at the cellular and molecular level, however, the research on cells and molecules as the main research object is still classified as cellular and molecular mechanobiology.

Cells are an important component of human tissues and organs, as well as the basic functional unit of human life. Cell proliferation, growth, differentiation, migration, apoptosis and other behavioral functions are regulated by cell microenvironment. Biochemical factors, ECM and adjacent cells are involved in forming the environment for cell survival; that is, the cell microenvironment, which can be divided into biochemical and physical microenvironments; the latter mainly includes the mechanical microenvironment. In the processes of cell growth, tissue formation, and disease progression, the cell mechanical microenvironment changes with time, and these mechanical changes also affect cell proliferation, differentiation and migration. In recent years, increasing attention has been paid to how the cellular mechanical microenvironment, such as matrix hardness, fluid shear stress, and matrix tension, affect cell biological behavior. One of the scientific problems that needs to be solved urgently is how cells respond and transfer extracellular mechanical stimulation signals into intracellular biochemical signals through mechanotransduction processes and what are the underlying molecular mechanisms. The process of cell-sensing, mechanical stimulation of the microenvironment, and regulation of cell behavior through mechanotransduction is closely related to force-sensitive receptors at the cell adhesion interface. Cells sense complex mechanics and regulate their own destiny through force-sensitive receptors that form the cell-ECM and cell-cell adhesion. Therefore, it is of great significance to reveal the molecular mechanism of force signal transduction mediated by force-sensitive receptors at the cell-ECM and cell-cell adhesion interface to understand how cells sense mechanical stimuli and how external mechanical stimuli regulate cell fate and other processes.

Integrin and cadherin are the most important mechanosensitive receptors on cell membranes, which mediate the mechanical interaction between cells and the surrounding matrix or adjacent cells, and transduce mechanical stimulation signals into biochemical signals, thus activating a series of intracellular responses, ultimately affecting cell differentiation, migration, and other functions. The mechanobiology of mechanosensitive receptors mediating stem cell differentiation and tumor invasion involves a series of mechanotransduction processes from cell membrane force-sensitive receptors to the cytoskeleton to the nucleus. Chen et al. established a force signal transduction mathematical model based on the mechanical theory of molecular adhesion by coupling the activation/aggregation dynamics of integrin molecules, the breaking and dissociation of the molecular bonds of integrin clusters, and focal adhesion kinase (FAK) phosphorylation on Y397 (FAKpY397) within integrin clusters. The modeling results predicted that integrin clustering dynamics governs how cells convert substrate stiffness to FAKpY397, and hence, govern how different cell types transduce mechanical signals. Existing experiments on cells confirmed the predictions and supported the model

(Fig. 4) [63]. These results reveal the mechanobiological mechanism of differences in the phosphorylation levels of FAK which depends on matrix stiffness, and suggest a new pathway by which integrin clusters enable cells to calibrate responses to their mechanical microenvironment.

Mesenchymal stem cells adopt differentiation pathways based on the cumulative effects of mechanosensing. A cellular mechanical microenvironment changes substantially over the course of development, beginning from the early stages in which cells are typically surrounded by other cells and continuing through later stages in which cells are typically surrounded by ECM. To adapt to the new environment, stem cells demonstrate differentiation behavior that depends on the stimulation of the past mechanical microenvironment, namely stem cell mechanical memory. How cells erase the memory of some of these mechanical microenvironments while locking that of others is unknown. Zhang et al. established a transcription factor relocation model based on the adhesion antagonism effect, and explored the mechanobiological mechanism of integrin (cell-ECM mechanical action) -cadherin (cell-cell mechanical action) co-mediating cellular mechanical perception and memory behavior [64]. From the perspective of the adhesion of cadherin antagonistic integrin to cytoskeleton stress unloading and ultimately the recovery of nuclear elastic deformation, they described the nucleo-mass relocation of transcription factor (YAP) and revealed the mechanobiological mechanism of cadherin-mediated erasure of cellular mechanical memory (Fig. 4) [64]. During mesenchymal development, the sources of mechanical forces transduced by cells transition over time, predominantly from cell-cell interactions to cell-ECM interactions. Transduction of the associated mechanical signals is critical for development, but how these signals converge to regulate human mesenchymal stem cells (hMSCs) mechanosensing is not fully understood, in part because time-evolving mechanical signals cannot be readily presented *in vitro*. Zhang et al. established a DNA-driven cell culture platform that can be programmed to present the RGD peptide from fibronectin, mimicking cell-ECM interactions, and the HAVDI peptide from N-cadherin, mimicking cell-cell interactions, through DNA hybridization and toehold-mediated strand displacement reactions [65]. The platform could be programmed to mimic the evolving cell-ECM and cell-cell interactions during mesenchymal development. They applied this platform to reveal that RGD/integrin ligation promoted cofilin phosphorylation, while HAVDI/N-cadherin ligation inhibited cofilin phosphorylation. Cofilin phosphorylation upregulated perinuclear apical actin fibers, which deformed the nucleus and thereby induced YAP nuclear localization in hMSCs, resulting in subsequent osteogenic differentiation (Fig. 4) [65]. Their programmable culture platform is broadly applicable for the study of dynamic and, integrated mechanobiological signals in development, healing, and tissue engineering.

With the development of mechanobiology research at the cellular and molecular levels, experimental methods need to be innovative. For example, immune checkpoint blockade with monoclonal antibodies (mAbs) targeting programmed cell death protein-1 (PD-1) has revolutionized cancer therapy. The binding kinetics determined by surface plasmon resonance do not always correlate well with their immunotherapeutic efficacy, mainly because of the lack of two-dimensional cell plasma membranes and the capability of force sensing and manipulation. Therefore, An et al. developed a Double-edge Smart Feedback control system as an ultra-stable platform to characterize the ultra-long bond lifetimes of receptor-ligand binding on living cells, based on a more suitable and ultra-sensitive biomechanical nanotool, biomembrane force probe (BFP) [66]. Their ultra-stable monomolecular force spectroscopy technique achieves ultra-stable control of mechanical stimulation and stable measurement of mechanically regulated molecular bond lifetimes in situ, at the monomolecular level in living cell membranes, with a 20-fold increase in the measurement stability. This ultra-stable BFP potentially provides a compelling kinetic platform for direct screening, optimization, and clinical selection of therapeutic antibodies in the future. They revealed the molecular mechanism of ligand recognition through mechanical regulation of the immune-activated receptor NKG2D by combining ultra-stable BFP, mathematical modeling, and computational biology, and proposed a novel concept that immunocostimulatory molecules also have certain recognition abilities [67]. They also used

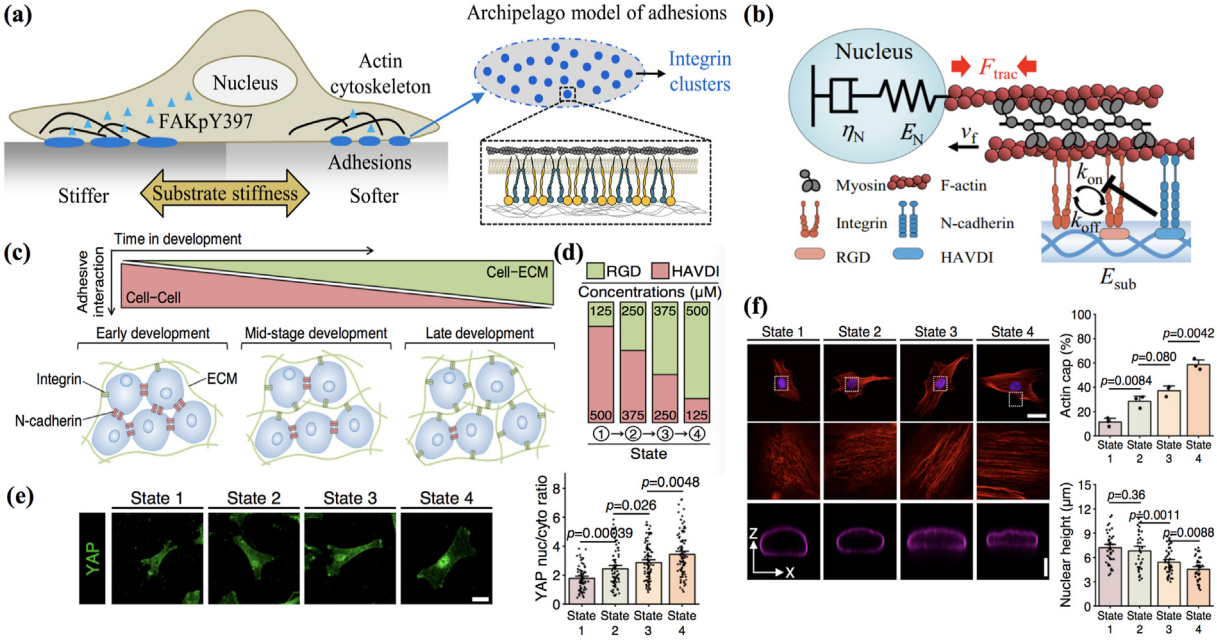

Fig. 4. Mechanotransduction mediated by transmembrane force-sensitive integrin and cadherin receptors. (a) The substrate stiffness controls phosphorylation of FAK through integrin activation and clustering Ref. [63]. (b) The scheme for motor-clutch model based on adhesion antagonism, where N-cadherin inhibits integrin-mediated cell-matrix adhesion and then affects actomyosin machinery Ref. [64]. (c) Schematic of the evolution of the mechanical microenvironment during mesenchymal development. (d) Schematic for achieving simultaneously increasing RGD and decreasing HAVDI on the substrates to mimic the mechanical microenvironment in (c). (e) Representative YAP images and quantification of YAP nuc/cyto ratios for the same conditions as (c). (f) Representative F-actin and Lamin A/C images as well as their quantifications in hMSCs for the same conditions as (c) Ref. [65].

single-molecule mechanical manipulation to reveal the pathogenic mechanism of the rapid and dynamic mechanically regulated allosteric activation of autoRNA recognition by mutation of the natural immune receptor RIG-I, which induces autoimmune diseases [68].

In recent years, COVID-19 abuse has attracted the attention of researchers in mechanobiology. The COVID-19 pandemic is caused by a novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Chen et al. revealed that the interaction force of polyvalent molecules mediated liquid-liquid phase separation by the SARS-CoV-2 nucleocapsid protein and RNA. This phase separation may provide important support for the formation and function of the SARS-CoV-2 replication core and facilitate viral assembly [69]. This study provides a new molecular mechanism for the assembly of SARS-CoV-2. By combining single-molecular force spectroscopy, molecular dynamics simulation, mechanical theoretical calculation, structural biology, and virology, they also revealed the molecular mechanism of the stable recognition of ACE2 and rapid activation of coronavirus spikes by sensing biomechanical factors and proposed a novel strategy to block viral invasion by locking the mechanical response of spikes [70].

These findings show that the development and breakthrough of mechanobiology need to rely on the integration of mechanics, biology, medicine and materials science. This will facilitate the step-by-step revelation of the mechanism by which cells sense mechanical stimulation of the microenvironment and regulate cell behavior through mechanotransduction. It makes us expect that in the future, the pathological microenvironment of living organisms could be improved by precisely targeting various force-sensitive receptors, so as to obtain more effective treatment.

5. Summary and perspectives

In conclusion, apart from the abovementioned research achievements, there have been many more research advances made by Chinese scientists in the field of mechanobiology, including biomaterials, immune cells, ophthalmology, and otolaryngology, in the last three years. Mechanobiology is an interdisciplinary discipline combining biology, engineering, chemistry, physics, and medicine. It is a comprehensive and high-tech discipline that focuses on how physical forces and changes in the mechanical properties of cells and tissues contribute to development, cell differentiation, physiology, and disease and allows for an understanding of the molecular mechanisms of mechanotransduction by which cells sense and respond to mechanical signals. Through these studies, we can further understand the physiological and pathological mechanisms of the human body, and discover new biomarkers or drug targets for the prevention and treatment of diseases to promote human well-being.

The core concept of the stress-growth law is the interplay and synergism between the mechanical micro-environment and the chemical micro-environment within cells. The results of mechanobiological studies, including mechanical, biochemical, cellular, and molecular mechanisms, will provide valuable information on the major mechanical and chemical factors in the organism. Consequently, mechanobiological studies should include the following: experimental approaches using animal models or clinical data *in vivo*; mechanistic studies at the cellular and molecular level *in vitro*; validation using gene manipulation approaches in disease models or model animals *in vivo*; further revalidation and implication using clinical samples; and gradual achievement of clinical transformation [16]. Therefore, two future suggestions for mechanobiology research indicate that studies on the mechanobiological mechanism of diseases should be conducted at the cellular and molecular levels to identify new biomarkers or potential targets for clinical transformation. Second, future mechanobiology research should strengthen the qualitative and quantitative combination of biological experiment and mechanical and mathematical modeling analysis, using mechanics as a simple, quantitative tool, to describe the mechanical problems in physiology with precise mechanical and mathematical language so that physiology can be as clear as physics, especially at cellular, subcellular and molecular scales.

At present, one of the trends in basic research in life science and medicine is to realize that physical factors, especially mechanical factors, and regulatory laws, play a very important role in biological processes and the occurrence and development of diseases. On the basis of traditional biomedicine, the study of biological processes and major diseases in the post-genome era will deeply explore the dynamic behavior of life phenomena to provide solutions to the major scientific problems in the field of life science and health, and provide important breakthroughs for the prevention and treatment of diseases and the improvement of human health.

Conflicts of interest

There are no conflicts of interest to declare.

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