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Biomechano-Interactive Materials and Interfaces

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Abstract:

The reciprocal mechanical interaction of engineered materials with biointerfaces have long been observed and exploited in biomedical applications. It contributes to the rise of biomechano-responsive materials and biomechano-stimulatory materials, constituting the biomechano-interactive interfaces. Here, we have briefed endogenous and exogenous bio-mechanical stimuli available for mechano-responsive interfaces and summarized their mechanistic responses, including deformation and volume change, mechano-manipulation of physical and chemical bonds, dissociation of assemblies, and coupling with thermoresponsiveness. The mechano-stimulatory materials, however, are capable of delivering mechanical cues, including stiffness, viscoelasticity, geometrical constraints and mechanical loads, to modulate physiological and pathological behaviors of living tissues through the adaptive cellular mechanotransduction. The biomechano-interactive materials

and interfaces are widely implemented in such fields as mechano-triggered therapeutics and diagnosis, adaptive biophysical sensors, bio-integrated soft actuators, and mechano-robust tissue engineering, which have offered unprecedented opportunities for precision and personalized medicine. Pending challenges are also addressed to shed a light on future advances with respect to translational implementations.

1. Introduction

The explosive development of biomedical materials with programmable functionality has significantly thrusted medical sciences and technologies, through modulating the biophysicochemical interactions at their interface. Conventionally, bioresponsive materials[1] respond to the pathophysiological conditions in a myriad of biomedical applications, including such innate biological signals and pathological abnormalities as pH,[2,3] redox,[4] hypoxia,[5,6] ATP,[7,8] glucose,[9,10] and enzymes.[11-13] In recent years, the biomechano-responsive materials emerge as a promising sub-category of bioresponsive materials to realize biomedical functions, such as drug delivery and healthcare monitoring, when subjected to biomechanical stimuli (body motions, heart beating, blood flow, *etc.*). It has aroused intensive efforts in developing high-performance biomechano-responsive materials by taking advantage of biomechanical stimuli (**Figure 1**) generated in such body actions as pushing, stretching, and bending, as well as the cellular contractility,[14-16] to activate the execution of programmed functionalities.[17] In the meanwhile, biological systems are also responsive to external mechanical stimuli, which have been exploited for thousands of years in traditional physical therapies (*e.g.*, cupping therapy, acupuncture, massage). However, the appreciation of the influence of mechanical stimuli on biological systems and the intricate cellular mechanotransduction have only emerged for decades since 1980s. Since the first use of silicone rubber to quantify tactile forces generated by single cells onto the matrix,[18] increasing microengineered tools have been developed to study biological

mechanoresponsiveness at the cellular or subcellular level,[19] which have revealed the ion channels sensitive to shear stress,[20] integrins and cytoskeleton responsive to magnetic bead twisting,[21] dictation of cell proliferation and apoptosis by geometrical constraints,[22,23] durotaxis of cell migration,[24] and regulation of matrix elasticity on stem cell differentiation (**Figure 2**).[25] Researchers have developed numerous materials to deliver customized single or multiple mechanical stimuli to the biological systems, which are defined as biomechano-stimulatory materials in this review.[17,26-28]

Put together, the robust mechanical interactions between the engineered biomedical materials and the biological systems constitute the biomechano-interactive interfaces, arising from the growth in biomechano-responsive materials and the biomechano-stimulatory materials (**Figure 3**). For biomechano-responsive materials, biomechanical stimuli are readily accessible, comprising endogenous compression/stretch *via* joint movements and internal shear force in vascular systems, as well as exogenous acoustic and magnetic force remotely applied through the skin. Compared to chemical or biological triggers, mechanical forces provide a relatively predictable control in direction and an adjustable magnitude management toward precise execution of functionalities. Since the first controllable release of therapeutics triggered by repeated compression in 2000,[29] intensive research efforts have contributed diverse implementations of biomechano-responsive materials, ranging from stretchable and flexible epidermal electronics,[30] ultrasensitive electromechanical sensor,[31] elastic drug delivery,[32] skin-inspired mechanoreceptor[33], to bio-integrated artificial stingray.[34] Meanwhile, biomechano-stimulatory materials have been employed to deliver mechanical stimuli, including stiffness and viscoelasticity, topographical and geometrical constraints, and mechanical loads (*e.g.*, stretch, compression, magnetic twisting), on the basis mechanoresponsiveness of tissues cells.[15,35] The mechanoresponsiveness of tissue cells are realized *via* the process of cellular mechanotransduction, in which the mechanical inputs can be translated into biochemical signaling. The studies of mechanobiology has revealed that

such mechanical cues and the cellular mechanotransduction can be influential in a variety of pathophysiological behaviors, such as apoptosis, division, migration and differentiation, as well as epithelial homeostasis and carcinogenesis.

The biomechano-interactive materials, including both the biomechano-responsive and biomechano-stimulatory materials, have significantly thrusted recent advances in fundamental biological sciences and biomedical engineering, ranging from mechanobiology, mechanically triggered drug delivery,[36] mechano-robust tissues engineering[37] and organs-on-chips,[38] as well as bio-integrated soft actuators.[39] Further efforts in developing such biomechano-interactive materials and interfaces with enhanced selectivity, sensitivity, stability and programmability will shed a light in the fields of fundamental mechanobiology, continuous healthcare monitoring, personalized medicine, and prosthetic bionics.

2 Multifaceted biomechanical cues at biointerfaces

Living tissues in the human body are generating active forces to interact with the residing microenvironment,[40] while undergoing various mechanical stimuli from the intrinsic microenvironment and external sources (Figure 1). In moving joints, muscles are generating tensile forces while cartilage and bones are bearing compressive loads through tendons. In blood vessels, the flowing blood are exerting continuous shear and hydrostatic stress on circulating cells and endothelial cells, which can also modulate the rolling and adhesion of red blood cells. During breathing and heart beating, tissue cells in the lung[41] and heart[42] are subject to cyclic stretch. In the meanwhile, viscoelastic and geometric properties of extracellular matrix (ECM) proteins can also influence cell migration and tissue organization.[37] For instance, stiffness gradients and structural organization of ECM proteins could direct the organization of cells in connective tissue and guide the alignment of myocardium during cardiovascular development.[19,43] Similarly, the collagenous matrix fibers appeared to facilitate the cancer metastasis spreading from a solid tumour site to

surrounding organs, in a synergy with stimulations of soluble factors.[44,45] More importantly, abnormalities in these biomechanical stimuli are clinical hallmarks of many diseases.[46] Tumour cells generally exhibit lower rigidity and cellular tension, whereas the cancer stroma has increased rigidity. Heart infarction is usually accompanied by weaker beating, while the obstructed blood vessels greatly increased the blood flow and shear stress. The collagen matrix in a connective tissue scar is poorly organized with dense parallel bundles. The intrinsic complexity and reciprocity of the aforementioned biomechanical cues and biological mechanotransduction therefore enable biomechano-interactive materials to actively and/or passively interact with biological systems. The biomechanical stimuli, including the endogenous forces (tensile, compressive, and shear forces) and the exogenous forces (ultrasound and magnetic forces), can be exploited as triggers for mechano-responsive materials to be interfaced with biological systems. On the other hand, mechano-stimulatory materials with engineered mechanical properties, including stiffness, viscoelasticity and geometrical constraints, can be tuned to modulate the pathophysiological conditions of residing tissue cells, therefore mechanically program such cell behavers as apoptosis, migration, division, differentiation and autogenesis.

2.1 Biomechanical stimuli for activating biomechano-responsive materials

The easy access to endogenous and exogenous biomechanical stimuli (**Table 1**) offers spatio-temporal and magnitude self-regulation of responses without requiring additional instruments. Taking drug delivery as an example, shear force of blood flows in vascular systems holds promise for non-invasive cardiovascular drug delivery.[47] Furthermore, on-demand feedback therapy can be triggered based on the disease pattern analysis when instrumented with blood flow/temperature sensor, data storage and transmission module.[48] Other endogenous and exogenous biomechanical stimuli are also exploited in a similar way, and are briefed below.

2.1.1 Endogenous forces: compression, tension and shear

Endogenous biomechanical forces include the compressive, tensile and shear forces, which are ubiquitous in the human body. Tensile forces are generated in the stretch of various muscles (e.g., cardiac muscles, smooth muscles and skeletal muscles), skin, tendons and bone joints, whereas compression are more typical in cartilage and bones. Shear forces can be found in the cardiovascular circulation system. These forces are necessary for maintaining physiological functions of living tissues and organs, such as heart beating, lung expanding, body motions, cold-stimulated capillary blood vessels contraction, *etc*.

Tensile forces are relatively more prevailing in the human body, stemming from flexing fingers and joints, stretched skin, muscle and tendons, beating heart, expanding lung and bladder, *etc*. The dynamic range of such tensile forces can vary from ultralow cell traction forces (~ 100 nN),[49] to maximal muscle forces (~675 ± 120 N).[50] Among tension-responsive biomedical systems, "elastic drug delivery"[51] is an innovative concept of stretch-triggered release of drugs or biologics.[36] Strain-dependent shape alternation and volume change can effectively control the drug release from either deformable elastomers or hydrogel matrices. Drug-laden mechanosensitive block copolymer micelles (BCMs) were covalently incorporated in poly(acrylamide) (PAAm)-based networks,[52] where the restricted BCMs provided the biomechano-responsive elements and the recoverable tension-induced deformation of BCMs led to drug release upon strain application (**Figure 4**a). In addition, the use of tension-induced crack propagation in polymeric[53], inorganic[54], and metallic[55] materials has also been demonstrated successful to achieve reliable responses to biomechanical stimuli. The cracks can be utilized for spatially controlled release of drugs or biologics. A stretch-sensitive superhydrophobic polymer composites, consisting of a hydrophilic mesh core and surrounding superhydrophobic layers with wetting resistance, was capable of drug release upon stretch-induced cracking.[53] Similarly, a multilayer film with a mechanotransductive surface for reversible stretch-triggered biocatalysis activation was also

developed.[56] In addition, thin metal films on elastomeric substrates show excellent reversible stretchability while remaining conductive, owing to microcrack formation.[55] The resistive changes during stretch can also be utilized to measure the subjected strain.[57] For instance, by forming nanoscale crack junctions, mechanical crack-based sensor mimicking a spider's slit organ exhibited ultrasensitivity with the gauge factor >2,000 within 0~2% strain.[58]

Compressive forces can be readily found in hand pressing, bone and cartilage during walk. Compression-responsive systems typically employ materials that can withstand high compressive forces, including the elastomeric substrates (*e.g.*, rubbers and silicones)[59] and the hydrogel. Given the biocompatibility, aqueous loading environment and tunable stiffness for proper mechanoresponsiveness, hydrogels are relatively more preferred for the *in vivo* delivery of therapeutics and biologics, as well as tissue engineering. One strategy is to incorporate soft and deformable micro-capsules (*e.g.*, liposome, micelles, vesicles) into the three-dimensional (3D) polymer network of the hydrogel. For example, dexamethasone (DEX) micelles was covalently integrated with hyaluronic acid (HA) hydrogel for pain management in osteoarthritic patients.[60] Owing to its hydrophobicity, anti-inflammatory drug DEX was trapped in lipophilic micelle cores and releases in a controllable manner, when degraded cartilage underwent compression during daily activities. As another typical example, a compression-sensitive system composing of calcium crosslinked alginate with physically-entrapped vascular endothelial growth factor for neo-vascularization was also reported.[29] Additionally, alginate hydrogels, when crosslinked with β-cyclodextrin, were endowed with responsiveness to compressive strain. The compression-caused deformation of the β-cyclodextrin moiety enabled the mechanoresponsive release of the inclusion complex through its multi-connectivity with the alginate matrix,[61] by destabilizing the inclusion complex and therefore decreasing ondansetron affinity to β-cyclodextrin (Figure 4b). It is equally noteworthy that mechanophores have been widely introduced into mechanoresponsive

materials.[62,63] A mechanochemo-sensitive elastomeric matrix embedded with mechanophores exhibited the capacity to load and release a furan derivative in response to physical stress.[64] The mechanophore with an oxanorbornadiene group could be activated upon mechanical stress, through the directed bond bending motion in polymer backbone by retro-[4+2] cycloaddition (Figure 4c). This could release s2mall molecules over multiple load cycles, with the potential of sequential release in a controllable manner. Furthermore, temperature increase of dissipative hydrogels under mechanical loads has also been coupled with thermoresponsive materials for controlled drug release. A mechanically-stimulated self-heating hydrogel composite, comprising of the highly-dissipative poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogel matrix and the poly(N-isopropylacrylamide) (PNIPAM)-based thermoresponsive nanoparticles, was capable of releasing the laden drug Xylene after 5-8 minutes cyclic compression, following the volume shrinkage of PNIPAM NPs triggered by the concomitant temperature increase (Figure 4d).[65]

Hemodynamic shear force, regarded as a crucial indicator of vascular (patho-)physiology, is a frictional drag force imposed by blood flow.[66] Normal vessels generally maintains a shear stress below 70 dyn/cm^2, while obstructed blood vessels are characterized by a dramatic increase in shear stress, which poses a threat to millions of people around the world for potential stroke and atherosclerosis.[67] Specifically, shear stress in a 95% constricted stenotic or thrombosed artery could reach above 1000 dyn/cm^2. Naturally, the increased local shear stress in the cardiovascular system constitutes one major stimulus exploited in the design of shear-responsive materials. Shear-responsive materials typically involve two types of responses, namely reversible shape deformation and dissociation of assemblies. One typical application is to utilize shear force-induced deformation of carriers to release therapeutics. Lenticular-shaped vesicles, prepared from a novel phospholipid 1,3-dipalmaminophospho-lipid (Pad-PC-Pad), could sense elevated shear stress.[47,53] The shear force could easily lead to breakage of Pad-PC-Pad liposomes within its equator, due to its lenticular geometry and

subsequent transient leakage of trapped cargos. The other strategy is to mimic the unique behavior of platelets, which sense and respond to the increased shear stress in injury regions by sticking to the vascular wall of injury regions, therefore aggregate locally and cease the bleeding. Microscale aggregates of nanoparticles have been accordingly developed,[68] which could remain intact in normal physiological flow but broke up into individual nanocomponents once activated by high shear force and then adhered and accumulated at stenotic regions (Figure 4e). The resulted increase in total exposed surface area of the particles therefore facilitated release of the payload that was immobilized on the nanoparticle surface. In addition, red blood cells (RBC) have been employed as promising endogenous candidates for drug delivery for decades. Heparin, an anticoagulant drug, was formed into nanoparticles via hybridization with polypeptide PLL.[69] These positively charged heparin nanoparticles (cNPs) could attach to red blood cells with negative charge *via* electrostatic attraction for long-term circulation. On thrombus sites, the shear stress significantly increased due to narrowing of the blood vessels, which led to site-specific release of cNPs from RBCs. With the help of RBCs as the drug delivery vehicle, the drug could then be delivered to target destinations with a prolonged circulation time.

2.1.2 Exogenous mechanical triggers: ultrasound and magnetic forces

Ultrasound, as a highly efficient and non-invasive trigger, has been widely explored for drug delivery and biomedical imaging.[70] Longitudinal pressure waves of ultrasound, are generated by transducers and transmitted into human body at 0.1~50 MHz frequency and amplitude with 0.01~10 MPa peak negative pressures.[71] This physical instrument could act as mechanical stimulus to activate ultrasound-responsive materials by pressure variation, cavitation and hyperthermia, acoustic fluid streaming and dissociation, enabling diagnosis and drug release.[72] A series of nano- to macro- architectures has been developed with ultrasound sensitivity such as micelles, liposomes, microbubbles, phase-change emulsions, microbubble-loaded hydrogels.[73] For example, a smart nano-network was able to regulate blood glucose

level (BGL) by ultrasound-triggered insulin release.[74] The gel-like cohesive network of 3D nano-scaffold was formed with alginate- and chitosan-coated poly(lactic-co-glycolic acid) nanoparticles (PLGA NPs) by electrostatic attraction, and both were loaded with insulin. The nano-network, which remained stably underneath the skin with tight adhesion of oppositely charged PLGA NPs, became partially dissociated and the diffusion of stored insulin from the microchannel in the porous scaffold when subjected to ultrasound (**Figure 5**a). Importantly, such dissociation-induced release behaviour could be tuned by ultrasound parameters such as input voltage, pulse duration, and ultrasound administration time.

Additionally, magnetic force induced by a magnetic field can remotely and non-invasively activate the magneto-responsive components.[75] To design efficient magnetic-sensitive materials, it is important to incorporate magnetic nanoparticles into polymer backbones, including supra-magnetic iron oxide (Fe_3O_4 or g-Fe_2O_3), metallic iron, or magnetic species (*e.g.*, Co, Ni, Fe). Paradigms of such magneto-responsive polymer composites include ferrogels and magneto-active elastomers. These magneto-responsive composites have been demonstrated with the potential of remote actuation (*e.g.*, contraction, deflection, orientation), guided delivery and release of biologics, and separation of biomolecules. On the basis of magnetic forces, microdevice with a "locking mechanism" based on polyethylene glycol (PEG) gel was developed for precise actuation and movement of freely moving components, in such applications as rotors, valves, pumps, manifolds, and delivery of payloads (Figure 5b).[76] The magnet with motorized rotation could act as a non-invasive and wireless external controller for this subcutaneously implantable microelectromechanical system device.

2.2 Mechano-stimulatory materials delivering mechanical cues

Besides aforementioned endogenous and exogenous biomechanical forces, the microenvironments of living tissues are equally full of such biophysical cues as varying elastic modulus and geometry of the ECM.[15] It is now well established that such biophysical

cues exert a profound influence on cell physiology (e.g., division,[77] migration,[49,78,79] differentiation[25,80,81]) and tissue pathology (e.g., tumorigenesis,[82] cancer metastasis,[40,83] lung fibrosis[84]). In the meanwhile, these mechanical cues are found to significantly vary in different tissues[14] and pathological conditions.[46,85] Therefore, these mechanical cues have been extensively recapitulated in the mechano-stimulatory materials and interfaces.

It is noteworthy that such influence can be reciprocal, meaning that the influenced cell behaviours can otherwise impose a difference in the ECM. For instance, increased stiffness of tumour stroma could facilitate the cancer metastasis, whereas the enhanced invasiveness, partially enabled by the activation of matrix metallopeptidase, also causes the ECM remodelling that also facilitates the "plasticity" of cancer invasion.[40] Therefore, such micro-environmental cues as elasticity and geometric constraints should also be considered in the design of biomechano-interactive interfaces.

2.2.1 Stiffness and viscoelasticity

ECM stiffness has been demonstrated to closely correlate with cell physiology and tissue pathology. Consistent with the varying stiffness of different living tissues (e.g., ~1 kPa of brain, ~10 kPa of muscle, ~100 kPa of collagenous bone), ECM stiffness per se is potent enough to regulate cell differentiation into neurogenic, myogenic and osteogenic phenotypes, when naive mesenchymal stem cells are cultured on synthetic hydrogel matrix with stiffness consistent with corresponding tissues (**Figure 6**a).[25] Gradient stiffness of the matrix is also capable of directing single cells to migrate from soft region into rigid region, which is termed as durotaxis.[24,37] Moreover, the collective migration is equally responsive to gradients of stiffness through the long-range intercellular force transmission, suggesting the collective durotaxis.[86] Also, the increased stiffness of tumor stroma might increase the malignance by integrin cluster modulation or mitogenic signaling elevation, using Erk and Rho-dependent cytoskeleton tension.[45,87] In addition to initial stiffness, such dynamic mechanics as viscoelasticity and partial stress relaxation of biological tissues (soft callus of remodelled

bone, liver, brain, adipose tissue, *etc.*) and ECM proteins (collagen or fibrin) are also influential on the physiology of residing cells.[88] Various natural or synthetic hydrogels and elastomers have been utilized to investigate the correlation of aforementioned mechanical properties with cell (patho-)physiology (**Table 2**).[89] Cell behaviors, such as spreading and stem cell differentiation, are found to be significantly different from those on elastic substrate with equal initial stiffness. For instance, spreading area of cells on soft viscoelastic substrates with stress relaxation was increased to the level of cells on stiffer elastic substrates, as compared to those on equally soft elastic substrates.[90]

2.2.2 Geometrical constraints

Micro-patterning[43] and nano-patterning[91] have been extensively exploited to investigate the effect of geometrical constraints on cell physiology. When microcontact printing was firstly introduced to modulate cell shape and function, it revealed that albumin secretion of hepatocytes reduced as the adhesive island size was increased and the cell growth was promoted.[22] Subsequently, suppressed cell death was also found to correlate with the increased spreading area of adherent cells, regardless of the adhesion area at the cell-matrix interface.[23] The width of patterned fibronectin stripes had a significant impact in the mode of epithelial migration, showing a switch from the swirling migration with 100 μm vortices in wide channels to a contraction-relaxation motion in narrow channels.[92] Also, the spindle orientation and division axis of HeLa cells was regulated by the underlying micropatterns, in terms of actin dynamics control and interfacial cortical component segregation.[93] Moreover, the muscle mimicking micropatterns with an intermediate aspect ratio (5:1 and 10:1) were found to promote the alpha smooth muscle actin expression and contractile output enhancement, revealing a cell traction force threshold of ~3.5 μN necessary for smooth muscle cell differentiation.[94] More recently, interfacial geometry has been revealed as a general trigger in the modulation of several human cancer stem cells (CSC).[82] Higher expression of CSC markers were found in regions of higher curvature in micropatterned cells,

which were also co-localized with such molecular markers of pluripotency as Nestin, Jarid1 and other transcription factors (Oct4, Sox2, Nanog). More interestingly, finite element analysis of the relative mechanical stress distribution within multicellular sheets revealed good correspondence between regions of increased mechanical stress and regions of high CSC marker expression (Figure 6b), suggesting the direct correlation of mechanical stress with cancer malignancy.

2.2.3 Mechanical load

In addition to the passive physical cues, tissue cells are also undergoing and responding to active mechanical loads, including cyclic stretch, shear stress and pressure. In such physiological conditions as breathing, heart beating and blood vessel pulsating, cells are undergoing cyclic stretching. While the endothelium is bearing continuous shear stress exerted by the blood flow, the airway epithelium and urothelium are subject to pressure from the contained air and urine, respectively.

A number of engineered platforms have been developed to impose mechanical loads on tissue cells, such as micro-aspiration, atomic force microscopy (AFM), magnetic twist or optical tweezer, which have been reviewed elsewhere.[19,95] In this review, we focus on those mimicking the physiological conditions with stretch and continuous shear stress, and the response of tissue cells to such mechanical loads. In response to the hours of cyclic stretching *via* the underlying elastomeric substrate, adherent REF52 fibroblast and the subcellular cytoskeleton (stress fibres) reoriented to a two micro-image angles, in contrast to naturally random orientations before stretching (Figure 6c). However, such sensitivity of tissues cells to external mechanical loads can be significantly different when they are stretched through the poroelastic natural matrices or hydrogels, which could rather undergo the hydraulic fracture of the epithelium.[96] Shear stress, as a result of the blood flow, imposes continuous and dynamic mechanical stimulus on endothelial cells (ECs), which can be converted into intracellular biochemical events and thereby influence cellular functions, including their

proliferation, migration, permeability, alignment and remodelling.[97] To deliver such mechanical stimulations, different modes of shear stresses are introduced, such as laminar, disturbed and oscillatory flows, recapitulating the temporal and/or spatial variations of the shear stress due to the pulsatile nature of the blood flow and asymmetric velocity profile, with the magnitude within 0-25 dyn/cm^2.

3 Mechanistic interactions at the interface

Biomechano-interactive interfaces involve the biomechano-responsive materials and biomechano-stimulatory materials. The former share a few, though not totally identical, basic responsive mechanisms upon biomechanical triggers, including the alteration in shape and/or volume, mechano-manipulation of the chemical or physical bonds, dissociation of assemblies, the coupling of mechano-responsiveness with other responsiveness, as well as the disruption of host-guest interactions and guided translocation/accumulation of magneto-responsive and/or shear-responsive materials (**Figure 7**). The latter is in a reciprocal development with the emerging recognition of cellular mechanotransduction. While many biomechano-stimulatory materials have been engineered for the studies of mechanobiology (*e.g.*, hydrogels with cell-adhesive micropatterns or tunable stiffness profiles, stretchable and biocompatible elastomer), the herein improved understanding of cellular mechanotransduction also increases the programmability of such mechano-stimulatory materials (*e.g.*, hydrogels with viscoelasticity or temporally-tunable stiffness). Together, the mechano-responsiveness of the former to biomechanical stimuli, in combination with the cellular mechanotransduction in response to the latter, constitutes the both sides of biomechano-interactive interfaces.

3.1 Mechanistic activation of biomechano-responsive materials

3.1.1 Shape and volume change

Deformation is a shared actuation mechanism for all three endogenous active biomechanical stimuli, namely tension, compression, and shear. Typically, elastomeric

rubbers and hydrogels, including the natural hydrogel (*e.g.*, alginate, hyaluronic acid (HA) chitosan, collagen, gelatin, *etc.*) and the synthetic hydrogel polymers (*e.g.*, poly(ethylene glycol), polyacrylamides, poly(vinyl alcohol), poly(hydroxyethyl methacrylate)), are bio-mechanoresponsive by altering their shape and/or volume. Additionally, the incorporation of deformable capsular component (micelle, microcapsules, or polymeric nanoparticles) of the device are equally widely exploited for drug delivery systems, providing higher drug loading capacity and an additional barrier to slow the diffusion of drug in the absence of a biomechanical trigger. These composites also separate the bulk mechanics from discrete agent encapsulation units, increasing the available choices for substrates. In both cases, "free drugs" are loaded into the matrix or deformable capsular component without direct bonding and released when subject to tensile, compressive or shear forces.

3.1.2 Mechano-manipulation of chemical and physical bonds

Mechanical force-induced chemical changes, including isomerization, ring opening, chain scission, and other intermolecular interactions can be useful in many biomedical applications, such as drug delivery, self-healing, actuators and sensors.[17,98] The incorporation of mechanophores is one widely exploited strategy for mechanical manipulation of chemical bond, though the scission or change in the mechanoresponsive chemical bonds is either irreversible or only reversible upon additional stimulus (*e.g.*, light, heat).[63] By contrast, the usage of physical bonding is reversible,[29] which allows for repeated execution of responsive functionality, such as self-healing.[99,100] Similarly, the mechanical effect on host-guest interaction is also reversible. Mechanical control of host–guest inclusion has been demonstrated by a mild mechanical stimulus, to realize controlled release of ondansetron, an anti-emetic drug, from a designed hydrogel composed of a β-cyclodextrin derivative and alginate.[61]

3.1.3 Dissociation of assemblies

Shear stress and ultrasound are capable of causing the dissociation of synthetic assemblies. Shear-responsive assemblies are sensitive to increased shear stress (1~2 orders in magnitude) in narrowed blood vessels, by dissociation of functional unit from the natural carriers (*e.g.*, red blood cell) or the pre-aggregated assemblies through relatively weak interactions (*e.g.*, electrostatic attraction). Similarly, ultrasound can also be remotely applied to disrupt such "weak" assemblies and cause its dissociation. This responsive mechanism is widely applied for injectable drug delivery system, for either the shear-stress trigger or the ultrasound trigger.

3.1.4 Coupling with other responsiveness

There are also quite a few paradigms combining biomechano-responsiveness with other responsive mechanisms, for instances, mechano-electrical responsiveness and mechano-thermal responsiveness. Mechanoelectro-responsive systems refer to those undergo changes in electrical properties (conductivity, capacity, *etc.*), which can be applied for developing wearable and implantable biomedical devices detecting such biophysical vitals as heart rate, pulses, body motions and breath. Typical examples include the stretch-sensitive micro-cracked metal film as strain sensor and compression-sensitive capacitive pressure sensor. Additionally, such mechanoelectro-responsive materials, when interfaced with electrogenic cells (*e.g.*, neurons, cardiomyocytes), can be employed to monitor the electromechanical coupling behaviors of the electrogenic cells, and to develop bio-integrated soft actuator which can simultaneously stimulate and monitor the cellular responses, and self-driven actuation. Meanwhile, piezoelectric materials have also been intensely exploited to generate power when subject to biomechanical stimuli, such as the triboelectric nanogenerator. It is also noteworthy that biochemical sensing can also be otherwise coupled with mechano-based transducing sensors showing unprecedented advantages, which has been already summarized.[101]

The mechano-thermal coupling is another effective strategy to achieve biomechano-responsiveness upon tensile forces when thermoresponsive units are incorporated. The dissipative properties of thermosensitive self-heating hydrogel has been employed as an internal heat source.[65] Thermoresponsiveness has been extensively exploited for drug delivery, anti-bacteria and responsive actuators. One classical paradigm is poly(N-isopropylacrylamide), which undergoes significant yet reversible shift between hydrophilicity and hydrophobicity upon heating. Importantly, the dissipative properties of hydrogels or elastomeric polymers can convert mechanical stimuli into heat. This combination of thermoresponsiveness and mechanoresponsiveness can improve the programmability (*e.g.*, sequential responses or orthogonal modulation) and reliability of the system. For example, the passive diffusion of the drugs encapsulated in the thermoresponsive microgels can be suppressed at the absence of stretch-caused heating. Also, magneto-responsive materials, once integrated with thermosensitive materials, can achieve a controlled release of cargoes by dissociation or morphology change of their carriers. The hydrogel matrix, formed with thermoresponsive nanoparticles, can produce self-heat after cyclic mechanical loading and cause a temperature increase, leading to shrinkage of the nanoparticles, followed by contents release.

3.2 Cellular mechanotransduction triggered by mechano-stimulatory materials

Mechanobiology is arising from the increasing recognition of the role of mechanical forces and cues in organogenesis and (patho-)physiological conditions of living tissues. This emerging field is dedicated to unravelling the underlying cellular mechanotransduction (**Figure 8**) that converts mechanical stimuli (*e.g.*, matrix stiffness and geometry, stretch or shear stress) into biochemical signalling involved in a diversity of cell behaviours and functions, ranging from apoptosis, proliferation, migration, division to epithelial homeostasis and tumorgenesis. Typically, the signalling pathway involves mechano-receptors at focal adhesions or cell–cell adhesions (*e.g.*, integrin, focal adhesion kinases, vinculin, cadherin,

catenin) and mechano-sensors (*e.g.*, talin and p130CAS), nuclear signalling factors (*e.g.*, nesprin, lamins), as well as other mechano-sensitive units (*e.g.*, actomyosin machinery, stretch-sensitive ion channels).[15] Given the mechanotransduction pathway, tissues cells can sense and respond to the mechanical stimuli as matrix stiffness and geometry via contractile actomyosin machinery and feedback reinforcement of integrin adhesions and cytoskeletons, mechanical stretch of the underlying substrate via cell-cell adhesions and integrin adhesions, as well as shear stress *via* the transmembrane stretch-sensitive ion channels. Importantly, these extracellular mechano-stimuli can be transmitted into the nucleus interior and DNA molecules through the coupling of cytoskeleton with the nucleus by newsprint and other outer nucleus membrane proteins (*e.g.*, nuclear lamins).[102] The timescale of such mechanotransduction varies from milliseconds to seconds for the unfolding of mechano-sensitive proteins, hours for altering the gene expression, days for changing cell physiology, and weeks for tissue morphogenesis. Abnormalities in the cellular mechanotransduction, either caused by mutations or dysregulation of involving mechanosensors or the altered cellular or extracellular mechanics, can contribute to the development of various diseases, such as muscular dystrophies and cancer progression or metastasis.

4 Implementations of biomechano-interactive materials

Biomechano-interactive materials and interfaces are currently of considerable interest because of their potential applications that range from tissue engineering, drug delivery, preventive healthcare, to soft robots (**Figure 9**). This can also be ascribed to the increasing recognition of the complex and hierarchical network of biomechanical stimuli and biological mechanotransduction. On one hand, these biomechanical stimuli can be employed to activate the biomechano-responsive materials and trigger the execution of programmed functionality (*e.g.*, force-triggered drug release, mechano-assisted diagnosis, adaptive biophysical sensor, and bio-integrated soft actuator), with versatile access and control in a spatial, temporal and

dosing management. On the other hand, mechano-stimulatory materials can introduce mechanical cues for constituting or recapitulating mechano-robust microenvironment for tissue engineering and mechanically-active organs-on-chips, mechano-assisted therapies and diagnosis.

4.1 Mechano-assisted therapeutic delivery and diagnosis

Biomechano-responsive therapeutic systems are promising in delivering enhanced treatment efficacy of diverse therapeutics in a spatiotemporal and dosage controlled way.[36] Easy access of biomechanical stimuli facilitates treatment in a variety of conditions with convenient commands. In occasions of emergence, such as heart attack and hypoglycemia, the mechanical force-mediated trigger could enable prompt delivery of therapeutics by patients in a self-administered manner. Recent advances in mechanically-triggered drug delivery system have also been outlined elsewhere.[36,59] The concept of "elastic drug delivery"[51] has been exploited to control the delivery dosage through a mechanically promoting mechanism. This strategy applies a self-accessible manner using daily body motion to release the pre-stored drug in micro-depots. The generated stretch during motion leads to Poisson's ratio-induced compression and deforms the microgels, achieving an on-demand release of drug.[32]

In addition, the skin permeability has to be enhanced, to achieve transdermal drug delivery. The key step to enable the permeabilized state is to transiently disrupt the outer layer of skin, called stratum corneum, with quite small thickness (normally below 20 μm).[103] So far, a number of approaches have been developed to break the skin barrier. Among these approaches, microneedles, have been widely investigated and demonstrated promising for delivering therapeutics or extracting fluid containing biomarkers for diagnosis.[104,105] When equipped with microneedle arrays, the "elastic drug delivery" was efficient in regulating blood glucose levels (BGLs) by stretch-triggered transcutaneous insulin delivery for type 1 diabetic mice. After several cycles of stretching and releasing, the BGLs of mice quickly

reduced to a normoglycemic level within half an hour. Meanwhile, pulsating regulation of BGLs was observed when the stretch was applied at 4 h intervals (**Figure 10**a). It is promising that diabetic patients can easily manage BGLs *via* simple joint movement, rather than the painful insulin injection. The combination of motions with temperature control can further enable a mechanical ablation method to achieve a novel technology for transdermal delivery.[106] The skin permeability is enhanced due to the microchannel and micropores, which are created by precisely delivered thermal energy from the contact between the skin and an array of high-temperature tip. It is worth noting low frequency ultrasound has also been utilized widely for transdermal delivery of drugs including therapeutic macromolecules.[107-109] It is generally accepted that the transport regions are created by microjet collapse of cavitation bubbles on skin. However, the ultrasound-induced skin permeability is usually not homogeneous, resulting in low percentage of transport regions formed in the treated skin surface. Optimizing the interfacial tension of the coupling medium could enhance the stability and population of cavitation bubbles, thus leading to larger area of transport regions.[71,110]

Although current implantable endovascular devices for angioplasty can effectively achieve the instantaneous recovery of blood flow, inflammation and failure of long-term re-endothelialisation have frustrated their clinical applications, and suppression of these side effects greatly rely on *in situ* diagnosis and therapy. This challenge can be addressed by integrating high performance, shear-responsive and bio-resorbable electronics. An integrative bio-resorbable electronic stent has been developed by recruiting a magnesium alloy stent decorated with ceria NPs, gold nanorods @ mesoporous silica nanoparticles (AuNR@MSN), rapamycin drugs, flow/temperature sensors, and a memory module.[48] The flow sensor monitors blood ow and the collected data is stored in the memory module for further diagnosis. Meanwhile, the combination of catalytic reactive oxygen species scavenging (ceria NPs) and hyperthermia-induced drug release (AuNR@MSN) allows for advanced feedback

therapy, based on the temperature sensor (Figure 10b). In this way, this suite of sensors and actuators can be endowed with multifunctionality, including flow monitoring, temperature measuring, data recording, wireless power/data transmission, inflammation treatment, responsive drug release, and hyperthermia therapy, as well as the offer of mechanical and structural support. We believe the future of such smart theragnostic platforms lie in the integration of sensors (biomechanical and biochemical sensing), data storage modules, responsive therapeutic elements, as well as wireless power and data communication in bio-resorbable constructs.

Biomarker identification is becoming increasingly important for clinical risk assessment, early detection of diseases, evaluation of therapy outcome, and the surveillance of recurrent diseases. However, the low concentration of biomarkers for such disease as cancer in serum hinders their use in early diagnosis. Therefore, it is necessary to develop probes capable of sensing cancer biomarkers at ultralow concentrations (10^6 times lower than other blood proteins). To address this challenge, a combined mechanical and optoplasmonic transduction in a hybrid assay for detecting ultralow cancer biomarkers as sparse as 1×10^{-16} g mL^{-1} in serum was develop.[111] Biomarkers (carcinoembryonic antigens or prostate specific antigens) were captured by an antibody anchored to the silicon cantilever surface and then by the antibody-tethered AuNPs in solution that recognize a free site of those biomarkers, in which the AuNPs functioned as a mass and plasmonic label. The silicon cantilever was used to detect these two signatures, which acted as a mechanical resonator and an optical cavity. This mechano-assisted assay significantly improves biomarker detection sensitivity and can be used in routine blood tests for early-cancer detection (**Figure11**a).

In the meanwhile, there is also an emergence in the systemic administration of exogenous agents to investigate biological states, in order to provide an alternative to endogenous biomarkers. Synthetic biomarkers (mass-encoded peptides bound to NPs) for non-invasive multiplexed urinary monitoring of disease have been accordingly constructed.[112] The

engineered nanoscale synthetic biomarkers passively aggregated in diseased sites with the host circulation. Upon reaching the targeted diseased site, their cleavage by aberrant proteases released the mass-encoded peptides into the host urine for the diagnosis of disease by mass spectrometry (Figure 11b). This approach has been applied to noninvasively detect early stage cancers and monitor liver fibrosis, which possesses the potential to be extended for multiplexed urinary monitoring in a wide range of human diseases.

Given the threat of bacteria to human health and such conditions as sepsis involving ultralow bacteria concentrations, there is a demanding need of efficient strategies for ultrasensitive detection and efficient elimination of pathogenic bacterial infections. Classic strategies, utilizing bacteria-targeting system comprising high-affinity molecules or antibodies to recognize specific bacteria to realize selective bacteria capture, however, suffer from low capture efficiency. To improve the efficiency, rapid mechanical interactions *via* the nanotopographical cues have been developed.[113] A strategy synergistically combined the effect of the nanotopographical interaction and specific surface functionalization of the 3D silicon nanowire array on bacteria adhesion, and enabled rapid and ultrasensitive bacterial detection as low as trace concentrations (10 colony-forming units/mL^{-1}) of pathogenic bacteria (Figure 11c). Such synergistic effect of mechanical nanotopographical interactions and the specific biochemical recognitions have also been leveraged in detecting the rare circulating tumour cells (CTCs), a biomarker of cancer metastasis (Figure 11d).[114] The accordingly enhanced capture efficient can be further boosted by introducing chaotic micromixer[115] and fractal nanostructures,[116] which both have increased the mechanical interactions of the CTCs with the substrate. Noteworthy, researchers have also exploited the mechanical properties of CTCs to separate them from the blood cells, such as the size, deformability and inertia.[117]

4.2 Adaptive biophysical sensors

A variety of biological signals, ranging from physiology (*e.g.*, pulse, , blood flow rate,

and temperature distribution), electrophysiology (*e.g.*, electroencephalogram (EEG), electrocardiogram (ECG), and electromyogram (EMG)),[118] as well as biophysical (e.g., strain, pressure, body motion)[54,119] and biochemical (*e.g.*, blood glucose and oxygen level, pH, and sweat metabolites) information, can be retrieved from the human body. These biological signals offer important clinical cues about normal organ functions, and the signs or progression of pathological conditions. There are remaining challenges, however, to continuously capture high-quality signal due to mismatch between the soft and mechanically robust living tissues and rigid and bulky characteristics of conventional medical systems. Therefore, biomechanically adaptive and responsive materials based device are necessary for retrieving such biological signals for preventive healthcare.

Continuous and high-fidelity monitoring of pulse, blood pressure, and heartbeat is essential as a primary aspect of health evaluation. Wearable strain and pressure sensors with high sensitivity are widely employed in skin-based devices to detect motions (*e.g.*, finger gestures and hand tremor), cardiovascular signals (*e.g.*, heartbeat rate, pulse shape, and blood pressures), respiration conditions, and mechanical properties of the skin. Recently, wearable health monitoring products have also been prevailing in the market, such as intelligent bracelets with real-time health monitoring of heart rate, impulses and blood oxygen level. Despite their popularity, the fidelity of the retrieved data is not as predictive.

Human body consists of many soft and curvilinear tissues with fine topology. Ultra-conformal contact onto such soft and curvilinear surfaces remains a challenge to realize high-fidelity health monitoring, which can be further complicated by the stretch, compression, bend or twist of the biological tissues. To achieve conformal contact without causing damage or inflammation, many efforts have been devoted to developing such soft bioelectronics devices in an ultrathin, laminated format and/or by virtue of intrinsically soft materials. These biomechanically adaptive devices have realized unprecedented performance in challenging scenarios, including electronic neural implants and optoelectronic devices. A soft and

implantable optoelectronic device, using the ultrathin hemispherically curved image sensor array and soft MoS_2-graphene, was established for optical sensing and retinal stimulation.[120] A skin prosthesis based on silicon nanoribbon, interfacing with the peripheral nerves, was capable of transmitting the mechanical/thermal signals from the prosthetic skin to brain.[121,122] Moreover, the soft neural/brain implants have successfully rehabilitated a rat with a disabled leg[123] and primates with spinal cord injury.[124] Meanwhile, taking advantage of the stretchable conductive network, various bioelectronic devices with high performance[125] and integrated multifunctionality have been demonstrated adaptable to such mechanical stretch, bend and twist. For example, electromechanical cardioplasty was accomplished through an elasto-conductive epicardial mesh comprising of highly-elastic styrene-butadiene-styrene rubber and highly-conductive silver nanowire, which resembled the innate cardiac tissues while restoring cardiac electro-conduction system. The elasto-conductive mesh wrapping the epicardial tissue was able to synchronize the myocardium while detecting cardiac electrophysiological signals of the robustly beating rat heart.[126]

Despite their high performance and conformity of these soft bioelectronics devices, biomedical devices that readily and intimately adhere to the skin and are simple to fabricate and robust for practical health prognosis remain less developed.[127] Inspired by the microhair architectures in nature, a highly skin-conformal microhairy capacitive pressure sensor was developed with the microhair interfacial structures amplifying the signal, which allowed maximal effective contact between the sensors and the irregular epidermis surface and therefore ~12 times higher signal-to-noise ratio (SNR) (**Figure 12**a).[128] Given such high SNR, the skin-conformal pressure sensor was even capable of monitoring weak signals from the deep-lying internal jugular venous pulses, allowing to tell waveforms of a healthy subject from one with cardiac diseases. Most recently, the ultrasensitive electromechanical sensor G-putty (gauge factor > 500) is developed mixing graphene with a lightly cross-linked polysilicon.[31] The obtained nanocomposites show uncommon electromechanical behaviour,

such as post-deformation temporal relaxation of electrical resistance and no monotonic changes in resistivity with strain (Figure 12b). It is extremely sensitive to such compressive and tensile deformation as found in joint motion, breathing, heart-beat, and pulses, and even impact of the footsteps of small spiders, which are ascribed to the motile nanosheets in the polymer matrix with low-viscosity.

Another challenge confronting the wearable and implantable biomechanical sensors is the robust stretch or compression incurred by the interfacing skin, heart or lung. To improve the SNR in such mechanically robust scenarios, typically exploited strategies include reducing the thickness down to tens of micrometers and bending rigidity and of the sensors, as well as enhancing the adhesion to the bio-interfaces.[129] Another strategy to adopt stretchable conductive network, including serpentine patterns, micro-cracked metal film, interweaved metal nanowire and wavy structures.[118] For instance, mechanically optimized serpentine patterns[130,131] can help soft network composites to match with the mechanical property of human epidermis, which provide better conformal contact and reduce effective impedance and noise for ECG monitoring. More importantly, this stretchable conductive network can adapt to the mechanical robustness of the interfacing tissues by deforming without disconnecting at a certain range. Given the improved SNR under mechanical robustness, these sensors with enhanced flexibility, stretchability and conductivity have been applied to map the elastic mechanical properties and hydration of skin.[132] These devices have given rise to the emerging field of epidermal electronics or e-skin, which integrates multiple sensing modalities without sacrificing the wearability.[30,133] Moreover, other functional modules such as the LED display and wireless communication units (RF coil) can be integrated into the epidermal electronic systems.[30]

In addition, structural substrate capable of redistributing the subjected strain has also been demonstrated promising. Thickness-gradient film of the carbon nanotubes were shown to be highly sensitive to strains with a gauge factor as high as 161 ($\varepsilon < 0.02$), while maintaining a

high uniaxial stretchability of more than 150%.[54] In addition to such modulation of the active layer, another microstructured fibre-shaped strain sensor decorated with intrinsic microbeads[134] is capable of redistributing the surface strain therefore enable an enhanced sensitivity regardless of the active materials (Figure 12c). Mechanical metamaterials have recently aroused much attention due to its unusual mechanical properties, such as the negative structural Poisson's ratio of auxetic metamaterials. When introduced into the strain sensors with conductive carbon nanotube network as the active component, auxetic metastructures can redistribute the strain in the conductive network and therefore increase the gauge factor to around 835 at ε=0.15 (Figure 12d).[135]

4.3 Bio-integrated soft actuators

Soft robotics has raised emphasis the optimization of material properties and novel actuation mechanisms,[136] with a shift from rigid components to soft materials,[137] as well as from external propelling to self-driving.[138] In line with this, several bio-integrated systems have been developed putting an emphasis on both aspects, including miniaturized walking machines,[139] flagellar[140] and jellyfish-inspired swimming devices.[141] These bio-integrated systems efficiently harvest energy from locally available nutrients by the integrated tissues cells, although a physiological solution is required.

One elegant paradigm is the artificial batoid fish that combines soft elastomer and tissue engineering with optogenetics, by patterning rat cardiomyocytes on an elastomeric body with a microengineered rigid gold skeleton (**Figure 13**a).[34] The artificial fish was equipped with a sensory-motor system, which allowed coordinated fin undulation and phototactically guided locomotion in response to light stimuli. The sequential activation of serpentine-patterned muscle circuits, induced by optical stimulation, led to coordinated undulatory swimming of the artificial fish. More interestingly, the optogenetically-engineered cardiomyocytes were also capable of discerning the light stimuli of varying intensity, enabling the versatile turning manoeuvring. In short, the combination of optogenetics and tissue engineering allows for

phototactic guidance, steering, and turning manoeuvres.

The cardiac microphysiological device could be further instrumented with piezo-resistive stress sensor to quantify the contractility of the "beating" of heart-on-chip.[42] Pioneering studies have contributed various cardiac patches,[142,143] however, the cardiac patches integrated with sensors for real-time monitoring is missing. A hybrid cardiac patch capable of *in situ* monitoring and regulating of the patch function was herein developed.[144] An electrospun nanofiber scaffold was employed as a 3D scaffold for cardiac tissue growth and tissue development. To provide electrical activation and spatial release of biochemical factors, as well as *in situ* monitoring of tissue function, multiple electrodes for monitoring tissue function were integrated with the freestanding, porous electronic mesh. Electroactive polymers were also incorporated onto the electrodes for controlled release of proteins and small molecules to promote tissue growth within the host. Considering that the fabrication needs multi-step lithography processes, another cardiac patch integrated with electronic sensors is fully developed through multi-material 3D printing (Figure 13b).[42] Specifically, six functional inks were exploited, featuring the piezo-resistive, highly-conductive, and biocompatible soft materials for the instrumentation of strain gauge sensors with optimal microgroove structures dictating self-assembly of laminar cardiac patches. One key feature of the design lied in the multilayer cantilevers, comprising of a base layer, an embedded thermoplastic polyurethane strain sensor, and a tissue-guiding microfilament layer. The cantilever deflection enabled by the anisotropic and synchronized contraction of the cardiac patch then induced the stretch at the strain sensor plane, which allowed for the quantification of the contractile stress by the resistive feedback. In both cases, the integration of mechanical sensors with bio-integrated soft actuator has enabled readily access to data acquisition to track the temporal development in tissue mechanics. Such instrumented bio-integrated soft actuators will also shed a light on tissue morphogenesis, pathogenesis, as well as the drug screening methodology.

4.4. Mechanically robust tissue engineering

Cellular traction forces[145] are employed by tissue cells to probe mechanical cues of the residing microenvironment, which are also within the range necessary for remodelling the extracellular matrices. In addition to geometrical constraints and initial stiffness, stress relaxation is another important feature of cell-ECM interactions and a key design parameter of biomaterials for tissue engineering. Herein, various hydrogels with tuneable stress relaxation properties have been developed for 3D culture, regardless of the initial stiffness.[90,146-148] It is found that gels with faster relaxation would promote the osteogenic differentiation of mesenchymal stem cells (MSCs), as well as cell spreading and proliferation. In rapidly relaxing hydrogels with an intermediate initial stiffness (17 kPa), MSCs also formed a mineralized, collagen-1-rich matrix similar to ECM found in bones. Such a mechanobiological response to stress relaxation of the residing matrices are attributed to feedback adhesion-ligand binding, actomyosin contractility and mechanical clustering of adhesion ligands.[149] In the meanwhile, sequential photo-degradation and photo-initiated crosslinking reactions to soften (from ca. 14 to 3.5 kPa) and then stiffen (from ca. 3.5 to 28 kPa) the hyaluronic acid-based hydrogels over a physiologically relevant range of stiffness (**Figure 14**a). Reversible mechanical signalling to adhered cells led to a decreased cell spreading and nuclear localization of Yes-associated protein/transcriptional coactivator with PDZ binding motif (YAP/TAZ) during softening, and an increased cell spreading and nuclear localization of YAP/TAZ upon subsequent stiffening.[150] In addition to such temporal remodelling, spatial recognition of the ECM mechanics is also revealed by such biological process as bone remodelling and cancer metastasis. The novel mechanotactic hybrids, developed by projecting lateral gradients of apparent interfacial stiffness onto the planar surface of a compliant hydrogel layer with a thickness gradient using an underlying rigid resin substrate with microstructures (Figure 14b), has found the collective durotaxis and mechanistic coupling with the ECM stiffness of ECM for the first time, independently of the

interfacial compositional and topographical cues.[86] The collective durotaxis of epithelial migration was ascribed to the enhanced long-range intercellular force transmission and the herein spatiotemporally orchestrated motions of individual cells. Likewise, photodegradable PEG-based matrix with spatially patterned stiffness has been exploited to direct stem cell fate, demonstrating the effect of spatial distribution and organization of subcellular matrix mechanical properties on cell behaviours.[151] Additionally, the guiding geometry of the underlying matrices also exerts a great influence on the efficiency of re-epithelialization across non-adhesive wounds through the formation of epithelial bridges.[152] Converging geometry was found to enhance the local orientational coupling of the stress fibres and epithelial migration and therefore promoted the re-epithelialization process, in contrast to the diverging geometry (Figure 14c).[78]

Interestingly, stem cells are also found to possess mechanical memory and the retained information of past mechanical dosing can be subsequently retrieved to regulate their differentiation.[153] It was found that previous culture history on stiff substrates (polystyrene; E~3 GPa) could significantly impact the fate of human mesenchymal stem cells (hMSCs) subsequently cultured on soft hydrogels (poly(ethylene glycol), E~2 kPa), including the activation of YAP/TAZ, as well as the pre-osteogenic transcription factor RUNX2. Also, a photo-tuneable PEG hydrogel was developed with the stiffness of initially 10 kPa (stiff) to 2 kPa (soft) upon UV irradiation. Consistently, the mechanical dosing of hMSCs cultured on initially stiff (10 kPa) substrates showed either reversible or irreversible activation of YAP/TAZ and RUNX2, depending on a threshold of such mechanical dose.

The concept of organs-on-chips has aroused intensive interest in both academic fields and pharmacy industry, taking into account their promising predictive power. Organs-on-chips, the biomimetic models of functional human organs, recapitulate the complex architecture of multiple cell types, biochemically and biophysically robust microenvironment, and physiological functionality of human organs, for example, liver, heart, lung, intestine, kidney,

brain, and bone. Typical organs-on-chips consist of transparent 3D polydimethylsiloxane (PDMS) microfluidic channel homing living tissue cells of the biological counterparts, and reconstitute three physiological characteristics of intact organs, including the 3D microarchitecture with the organization of multiple tissue types, the functional interaction at the tissue–tissue interface, and sophisticated mechanical and biochemical microenvironments of the specific organ.[38]

Various types of mechanical stimuli induced by physiological flow (e.g., blood flow and interstitial flow) and tissue actions (*e.g.*, breathing, peristalsis, and heartbeat), including fluid shear stress, tension, compression, has been reproduced in organs-on-chips by introducing fluid motions and cell culture substrate deformation. In a biomimetic lung-on-chip,[41] cyclic stretch was recruited to recapitulate the functional alveolar-capillary interface of the human lung (**Figure 15**a). The reconstituted lung-on-a-chip unveiled an accentuated toxic and inflammatory responses upon exposure to silica nanoparticles and bacteria. The cyclic stretch also enhanced the uptake of nanoparticles by epithelial and endothelial and stimulated their transport into the underlying microvascular channel, similar to the effect observed in whole mouse lung. By virtue of this mechanically active lung-on-a-chip, the organ-level disease model, mimicking drug toxicity-induced pulmonary edema in cancer patients with interleukin-2 treatment, revealed mechanical forces in physiological breathing can contribute the vascular leakage and thereby the pulmonary edema, independently of circulating immune cells (Figure 15b).[154] In addition, the deleterious fluid mechanical stresses, caused by the propagation and rupture of liquid plugs, was found to induce injury of airway epithelial cells by stimulating the surfactant-deficient opening of closed airway (Figure 15c).[155] Mechanically active “organs-on-chips” with resembled functional tissue-tissue interfaces may therefore expand the capabilities of cell culture models and provide low-cost alternatives to animal and clinical trials for drug discoveries and pathophysiology studies.

5 Conclusions and perspectives

Biophysicochemical interactions at interface of engineered materials and biological entities have been extensively exploited in various biomedical applications, such as cancer diagnosis,[156] feedback therapy,[157,158] and wearable sweat sensing.[159,160] The emerging mechano-responsive materials also show unprecedented properties, giving rise to the development of mechanophores and mechanochromic materials.[62,63] Given the recognition of biomechanical cues, there arises the sub-class biomechano-responsive materials, which can be activated by either the endogenous biomechanical forces (tension, compression, and shear,) or the exogenous mechanical forces (ultrasound and magnetic forces). In the meanwhile, biological responsiveness to mechanical properties of interfacing materials and the underlying cellular mechanotransduction have been gradually been recognized. The herein rising field of mechanobiology has revealed that biological systems (e.g., tissue cells and functional organs) are sensitive to such mechanical stimuli as stiffness, viscoelasticity, geometrical constraints and mechanical loads (e.g., cyclic stretching and shear stress). Therefore, a diversity of mechano-stimulatory materials has been developed to deliver such mechano-stimuli, for constructing mechano-robust physiological or pathological microenvironments. The incorporation of biomechano-interactive interfaces has greatly advanced the categories of programmable drug delivery, wearable and implantable healthcare monitoring, bio-integrated soft actuators, and robust tissue engineering. Nonetheless, several challenges need to be solved before clinical translation of such biomechano-interactive materials.

For mechanically-triggered drug delivery, one major concern of the bio-mechanoresponsive system is the substantial burst release. It is still challenging to realize precise control of drug dosing. Due to a relatively complicated combination of passive release and dynamically triggered release, it is difficult to regulate the released dosage in a repeatable manner, which becomes even more challenging for long-term administration in a physiological environment. A delivery system with confined drug amounts or with a

"rechargeable" mechanism could potentially avoid the risk of side effects due to overdose. Second, for shear-sensitive drug delivery system, how to prolong the circulation time by modifying the surface and how to enhance specific delivery by using targeted ligands are two of the main difficulties that need to be addressed. Third, one obstacle, when considering magnetic guidance for intravenous administration, that should be overcome is the high blood flow rate (> 10 cm/s in arteries and > 0.05 cm/s in capillaries). Providing strong magnetic fields could be one solution to remotely manipulate magneto-responsive materials against diffusion and bloodstream. To further extend the practical applications of the magneto-responsive materials, it is also important to provide magnetic fields with improved homogeneity and increased effective distance.[75]

The incorporation of nanotechnologies, stretchable and flexible electronics, self-powered systems, and wireless technologies have been driving innovations in wearable medical devices at a tremendous pace, giving rise to the conceptual epidermal electronics and electronic skin.[122] These recently developed wearable medical devices, composed of flexible and stretchable materials in the laminated format, have the potential to be conformably interfaced with the human skin, therefore allowing high-fidelity bio-data retrieval, continuous health monitoring and preventive diagnosis. Unfortunately, the ideal "second skin-like" adhesion between the wearable devices and the human skin is not yet fulfilled to leverage the promised potential. Reliable adhesion is necessary to withstand and sense robust body motions for the practical realization of mobile health care of wearable devices.[128] Herein, we propose "conformal adhesion" as the next challenge beyond conformal contact. To address this challenge, a myriad of nature-inspired strategies[161] could be exploited, such as the micro/nano-fibrillar structures on the feet of geckos,[162] adhesive toe pad of tree frog,[162] octopus suction cup-inspired adhesion,[163,164] mussel-inspired[165] and slug-inspired[166] wet adhesive, or a combination of both geckos-inspired structure and mussel-inspired surface modifications.[167] Briefly, the introduction of covalent bond, physical interlocking, negative

pressure, electrostatic attraction, as well as energy dissipation[166] or stress redistribution units[168] can enable stronger adhesion. Another challenge confronted with wearable and implantable devices lies in wearing comfort and the long-term biocompatibility respectively. For implantable devices, inflammation or thrombosis constitutes a major threat, even for such materials conventionally believed to be biocompatible as PDMS.[138] For wearable devices, however, gas permeability and skin rash is a threatening problem for long-term usage.[169]

Meanwhile, mechanically adaptive data storage and transmission are also necessary in continuous monitoring of biophysical information for further health or disease evaluation and delivery of feedback therapy. Accordingly, ultrathin data storage modules and mechanically deformable memory modules have been integrated into wearable and implantable biomedical devices, which have imparted high-performance non-volatile data storage modules to exhibit. This allows rational designs for the integration of individual electronic devices to exhibit a series of functions, such as sensing, memory, and feedback.[129] A motion memory device would be able to monitor and memorize various body motions. When attached to the joints of limbs, the motion memory device can detect the deformations caused by limb motions and simultaneously store the corresponding information in the memory device, in which memory devices and stretchable strain sensors can be integrated as a single module.[170] Also, feedback therapies towards motions disorders can be realized by further incorporating the therapy functionality. One multifunctional system for delivering feedback therapy integrated a wearable nonvolatile memory module with a Si NM-based strain gauge array, which measured strain changes for tracking tremors of patients with Parkinson's disease.[171] The tremor frequencies could be stored in memory cells and then analyzed to evaluate patient conditions, while the stored data can subsequently be analyzed to diagnose patient conditions. Importantly, ultrathin data storage modules and mechanically deformable memory modules based on metal or semiconducting materials can fail after cycles of deformations and accumulate fatigue. One strategy is to utilize soft nanomaterials (*e.g.,* carbon

nanomaterials[172]) to impart mechanical reliability, without undergoing mechanical fractures during skin deformation.

In order to implement fully biomechanically adaptive bioelectronics systems, flexible and stretchable energy supply modules are also on demand. Typically, micro-/nano-materials with large surface area and tunable deformability, allowing more reaction sites for energy generation and storage and high mechanical deformability, are exploited to develop such energy supply modules. Being in conformal contact with the human body, these energy supply modules can harvest and store energy from body motions, residual heat, or light. One typical strategy is to employ piezoelectric materials to harvest the energy from the mechanical vibrations of body motions and generate electric power. For instance, an elastic piezoelectric nanocomposite, blending piezoelectric micro-particles with MWCNTs in silicone substrates, is capable of generating stable electric power upon mechanical stimuli.[173] Another promising strategy is to incorporate triboelectric generator that harvests the energy from triboelectrification effect in a wearable format, which can be promoted by increasing the friction and effective contact area through nanomaterials.[174] Despite recent advances in the energy harvesting efficiencies of piezo- and tribo-electric generators, continuous power supply with higher currents and storage capacity remains challenging. The integration of continuous and highly-efficient energy harvesting and storage modules would allow self-powering of wearable and implantable bioelectronics systems.

When it comes to bio-integrated soft actuators or mechanically active “organ-on-chip”, the sustained viability and functionality of the recruited living tissue cells is a tough challenge for long-term applications. In the physiological microenvironment, homeostasis is well maintained by the removal of unhealthy cells and renewal of specifically differentiated stem cells.[175] However, most of current bio-integrated soft actuators are single type cells (e.g., smooth muscle cells or cardiomyocytes[39,42]), which are incapable of self-renewal. Also, unhealthy or dead cells can release unfavourable growth factors, which should be cleared

timely, in a way similar to the immune-system. Meanwhile, stimulation of these integrated tissue cells with spatiotemporal programmability is another challenge before the bio-integrated actuators can fulfil more complex commands. In the biological systems, motor neurons are specialized to stimulate the action of motor units of muscles. It would be interesting if the integrated tissue cells can be dissected into elementary units, which can be controlled independently by such commands as optical or electrical stimuli.

Extending beyond mechano-responsive and mechano-stimulatory materials, here we would also propose the concept of mechano-fabricated materials, namely those with excellent properties enabled by additional mechanical forces during fabrication, such as pre-stretching,[118] magnetic stirring,[176] and kirigami.[177,178] Furthermore, would it be accessible to obtain mechano-fabricated materials by taking advantage of biomechanical stimuli, since the (patho-)physiological microenvironment is full of endogenous mechanical forces? Would the resulted biomechano-fabricated materials be more adaptive to the biomechanical stimuli, therefore allowing a better interaction with the residing environment? In other words, would the biomechano-responsiveness of these materials be better matched with the interfacing biological tissues?

In the meanwhile, the introduction of other advanced fabrication techniques is on demand for a better recapitulation of the hierarchical architecture of biological systems. Biological materials, such as mineralized bones and teeth, usually comprises of stiff (*e.g.*, calcium salts) and compliant materials (*e.g.*, proteins, polysaccharides) with feature sizes ranging from nanoscale to macroscale, and possess unique mechanical characteristics combining the strength and toughness. However, synthetic materials have encountered challenges in recapitulating the natural counterparts.[179] To address these challenges, freeze casting and 3D printing are two promising strategies. Freeze casting uses microstructural ice templates to confine ceramic suspensions and to fabricate porous and layered materials. 3D printing, including 3D inkjet printing, fused deposition modeling, stereolithography, has been applied

to make complex architectures out of one single "ink" or multiple "inks". 3D printed moulds has been used to construct biomechano-stimulatory environment and reveal collective durotaxis of epithelial cells for the first time.[86] It could also customize shape memory composites with photo-thermal conversion to that fabricate photoresponsive actuator.[180] The potential of 3D printing, with the increasing diversity of printable materials and printing resolution, will be further leveraged in recapitulating hierarchical architectures composed of multiple biological materials with differential properties.

In summary, we have profiled biomechano-interactive materials and interfaces, comprising of biomechano-responsive materials and biomechano-stimulatory materials, with regards to the accessible biomechanical stimuli, diverse mechanisms of mechanoresponsiveness and cellular mechanotransduction, as well as their implementations in such applications as tissue engineering, therapy, diagnosis, and the soft actuator. Besides advances in these aspects, we have also identified challenges for the implementations of biomechano-interactive interfaces to fully leverage their potential by improving programmability with respect to specific biomedical applications. We believe the biomechano-interactive interface is a promising candidate for advancing smart and personalized pharmacy and healthcare industry.

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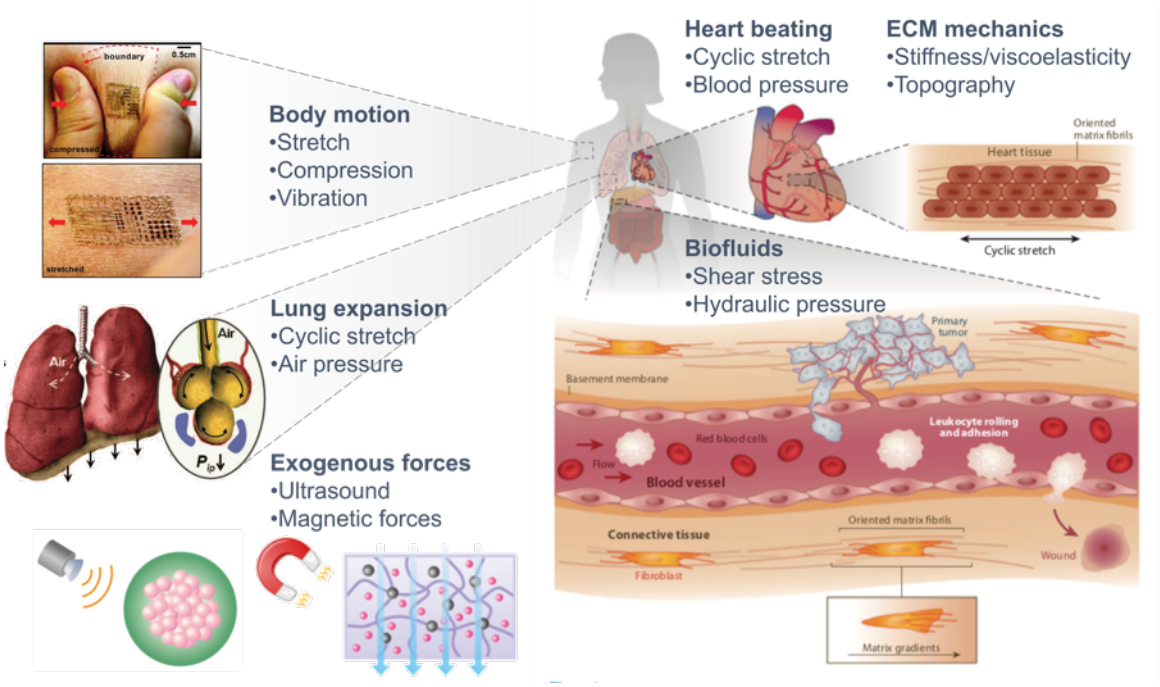

Figure 1. The complex network of mechanical cues at the biointerfaces. Body motion. Reproduced with permission.[30] Copyright 2011, AAAS. Heart beating, biofluids, and ECM mechanics. Reproduced with permission.[19] Copyright 2009, Annual Reviews. Lung expansion. Reproduced with permission.[41] Copyright 2010, AAAS. External forces. Reproduced with permission.[36] Copyright 2016, American Chemical Society.

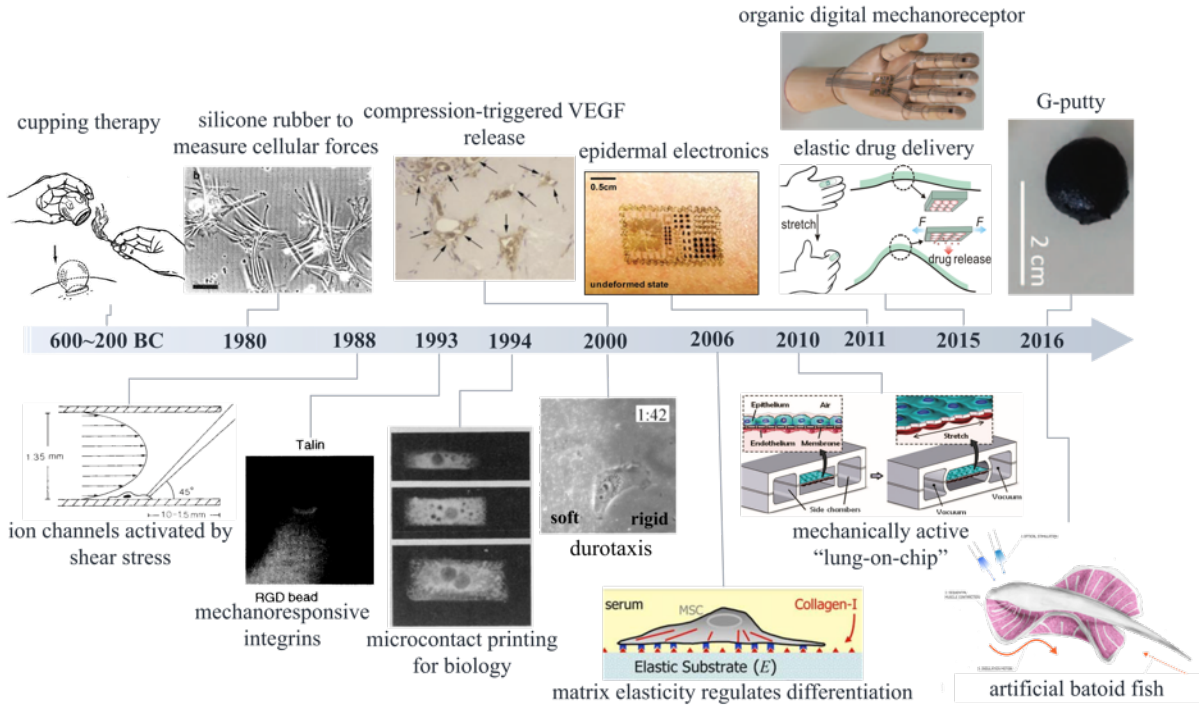

Figure 2. Timeline of milestones in unveiling mechanical interactions of the biology systems with engineered materials. *Cupping therapy.* Reproduced with permission.[181] *Silicone rubber to measure cell forces.* Reproduced with permission.[18] Copyright 1980, AAAS. *Ion channels activated by shear stress.* Reproduced with permission.[20] Copyright 1988, Nature Publishing Group. *Mechanoresponsive integrins.* Reproduced with permission.[21] Copyright 1993, AAAS. *Microcontact printing for cell biology.* Reproduced with permission.[22] Copyright 1994, AAAS. *Durotaxis.* Reproduced with permission.[24] Copyright 2000, Elsevier Ltd. *Compression-triggered VEGF release.* Reproduced with permission.[29] Copyright 2000, Nature Publishing Group. *Matrix elasticity regulates differentiation.* Reproduced with permission.[25] Copyright 2006, Elsevier Ltd. *Mechanically active "lung-on-chip".* Reproduced with permission.[41] Copyright 2010, AAAS. *Epidermal electronics.* Reproduced with permission.[30] Copyright 2011, AAAS. *Elastic drug delivery.* Reproduced with permission.[32] Copyright 2015, American Chemical Society. *Organic digital mechanoreceptor*. Reproduced with permission.[33] Copyright 2015, AAAS. *Artificial batoid fish.* Reproduced with permission.[34] Copyright 2016, AAAS. *G-putty* Reproduced with permission.[31] Copyright 2016, AAAS.

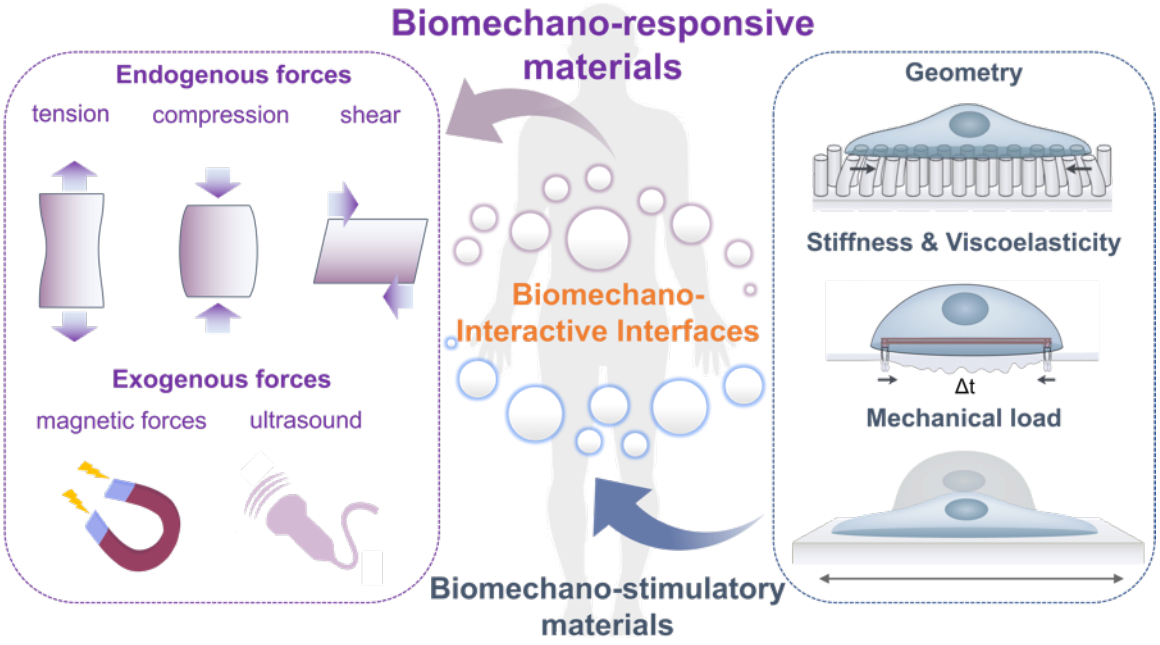

Figure 3. Biomechano-interactive interfaces comprising of biomechano-responsive materials and biomechano-stimulatory materials. *Left*, biomechanical forces ubiquitously found in human body for activating biomechano-responsive materials, including such endogenous forces as tensile forces, compressive forces and shear forces, and such exogenous forces as ultrasound and magnetic forces to remotely interact with ultrasound-responsive and magneto-responsive materials. *Right*, mechanical inputs imparted by the biomechano-stimulatory materials, including the geometrical constraints, stiffness and viscoelastic properties, as well as mechanical load.

Table 1. Typical magnitude of endogenous and exogenous biomechanical stimuli

Types of stimuli	Magnitude	Ref.
Biomolecular motors	Myosin V: 3 pN; Kinesin/Dynein: 7-8 pN; Bacterial flagella motor: 4000 pN*nm	[182]
Cell traction forces	Madin-Darby Canine Kidney cells: ~1.6- 12.7 kPa; Non-metastatic MCF 10A: ~ 150 nN; Metastatic MB231: ~ 300 nN; NIH 3T3 (3D culture): 0.1-5 kPa;	[183-185]
Body motions	Brain: up to ~ 20% strain; Spinal cord: up to ~ 20 % strain; Muscle stretch: up to ~ 30 % strain; Skin stretch: up to ~80 % strain; Normal blood pressure: 80-120 mm Hg	[127]
Flow shear	Mean wall shear stress: 8-16 dyn/cm^2 Normal blood vessel: 70 dyn/cm^2; 95% constriction: > 1000 dyn/cm^2	[186,187]
Ultrasound	Low frequency: 20-100 kHz; High frequency: > 1 MHz Pressure amplitude: ~ 0.6-2 MPa	[188]
Magnetic forces	Magnetic field strength (H): ~1-10^3 kA/m	[75]

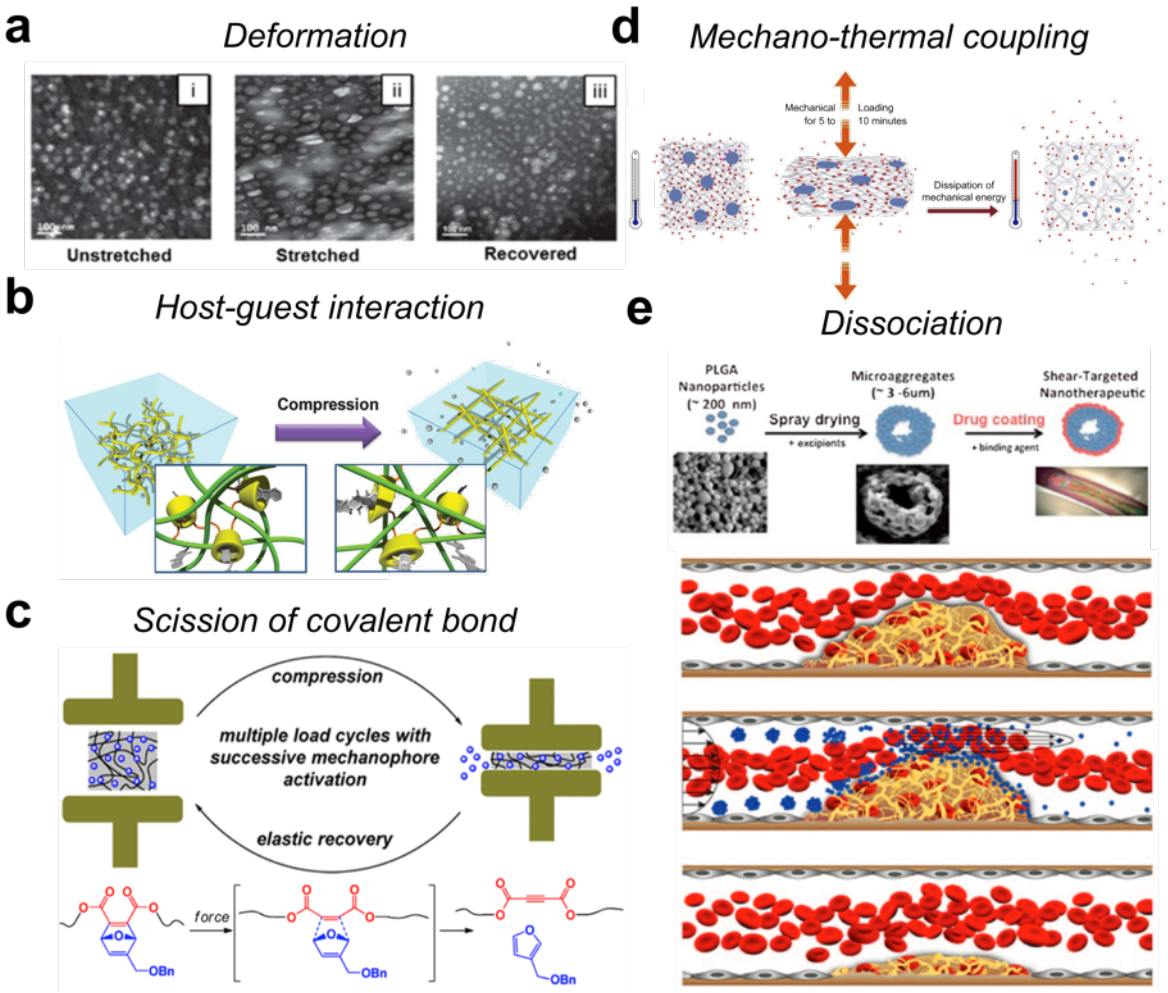

Figure 4. Activation of biomechano-responsive materials through endogenous biomechanical forces. a) Stretch-responsive hydrogels crosslinked by block copolymer micelles. Reproduced with permission.[52] Copyright 2012, The Royal Society of Chemistry. b) Controlled release of ODN from a hydrogel composed of a CyD-containing molecular network by mechanical compression. Reproduced with permission.[61] Copyright 2013, The Royal Society of Chemistry. c) Oxanorbornadiene-based mechanophore capable of successively releasing small organic molecules from a cross-linked network upon repeated compressions. Reproduced with permission.[64] Copyright 2014, American Chemical Society. d) Mechanically-stimulated thermosensitive self-heating composite hydrogel with controlled drug release. Reproduced with permission.[65] Copyright 2013, Elsevier Ltd. e) Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels. Reproduced with permission.[68] Copyright 2012, AAAS.

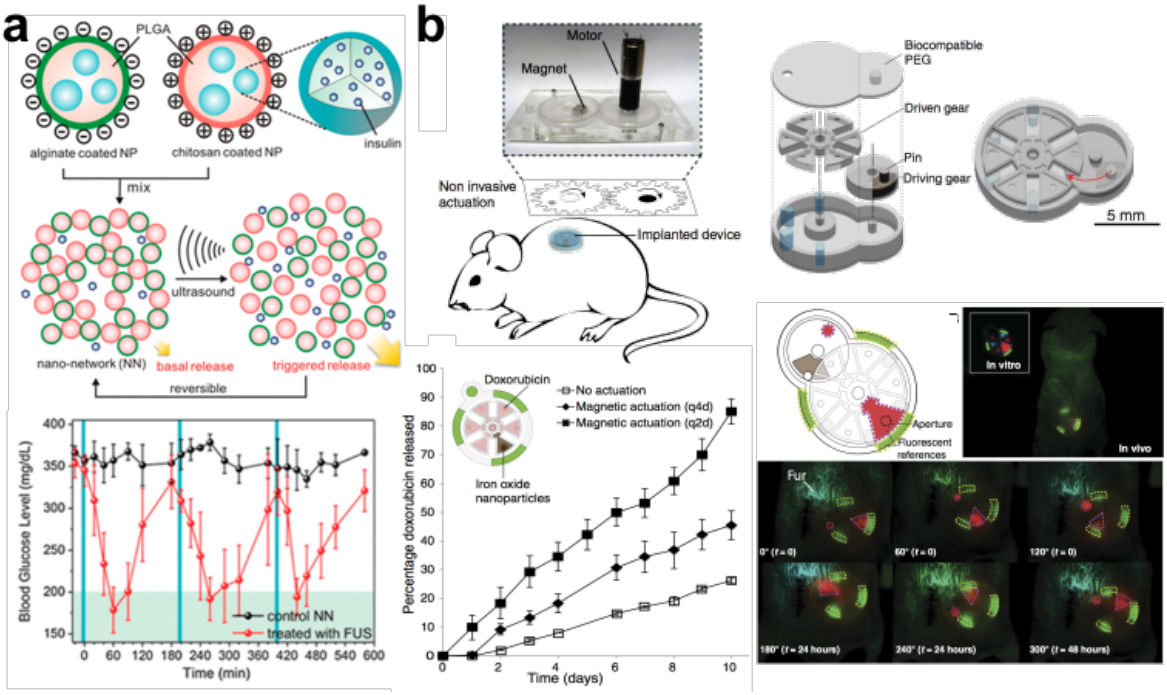

Figure 5. Exogenous mechanical triggers for mechano-responsive materials in controlled drug release. a) Ultrasound-mediated insulin delivery system using a nano-network comprising of negative charged alginate-coated NP and positively charged chitosan-coated NP. Reproduced with permission.[74] Copyright 2014, Wiley-VCH. b) 3D printed implantable microdevices for magneto-responsive release drug payloads, on the basis of "locking mechanism" for precise actuation. Reproduced with permission.[76] Copyright 2017, AAAS.

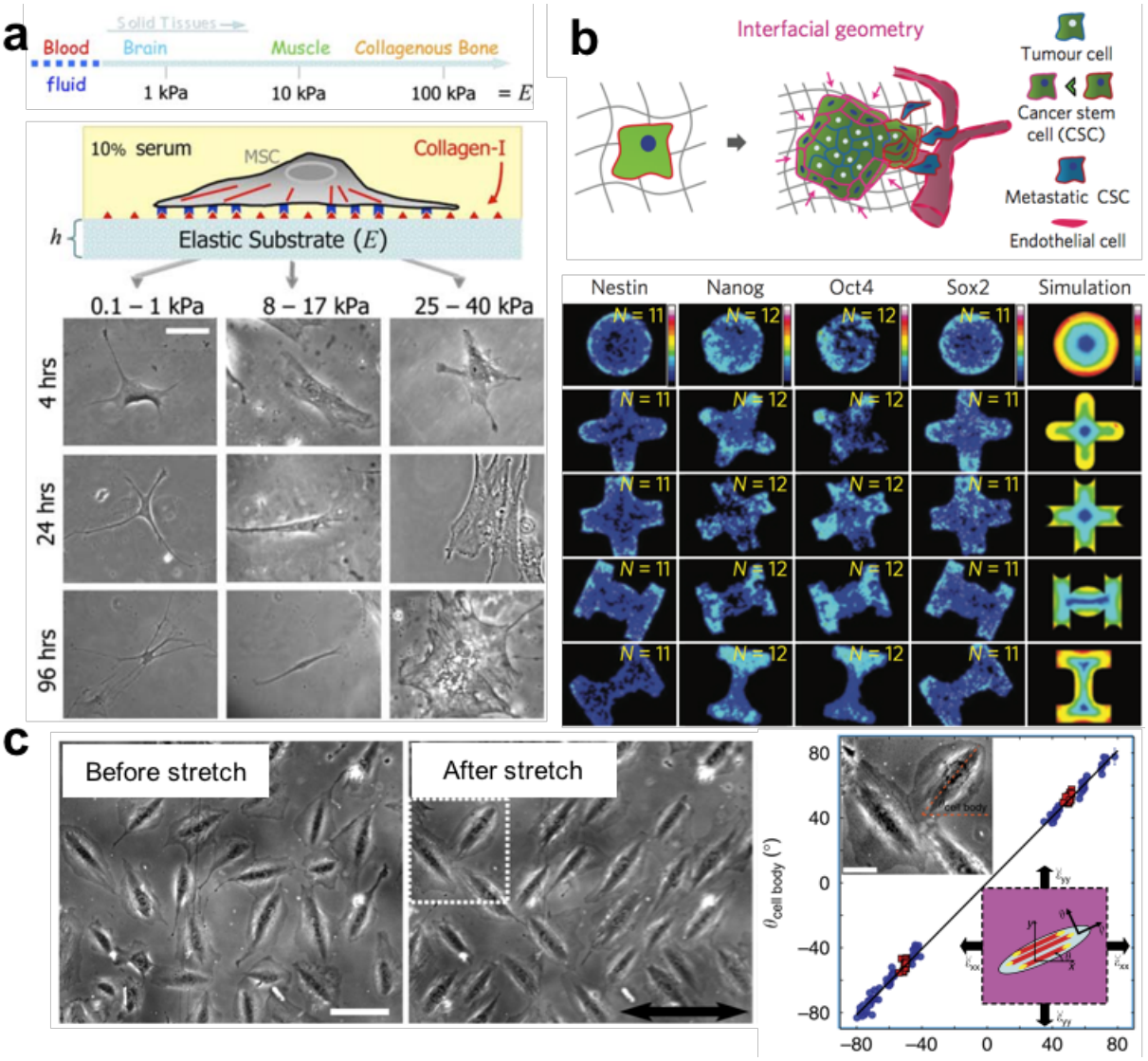

Figure 6. Influence of biophysical stimuli of the (patho-)physiological microenvironments on cell behaviors. a) Stem cell differentiation mechanically dictated by substrates of corresponding ECM elasticity. Reproduced with permission.[25] Copyright 2006, Elsevier Inc. b) Cancer cell tumorigenesis determined by the interfacial geometry, curvature and mechanical stress. Reproduced with permission.[82] Copyright 2016, Nature Publishing Group. c) Endothelial cell orientation under cyclic stretching. Reproduced with permission.[189] Copyright 2014, Nature Publishing Group.

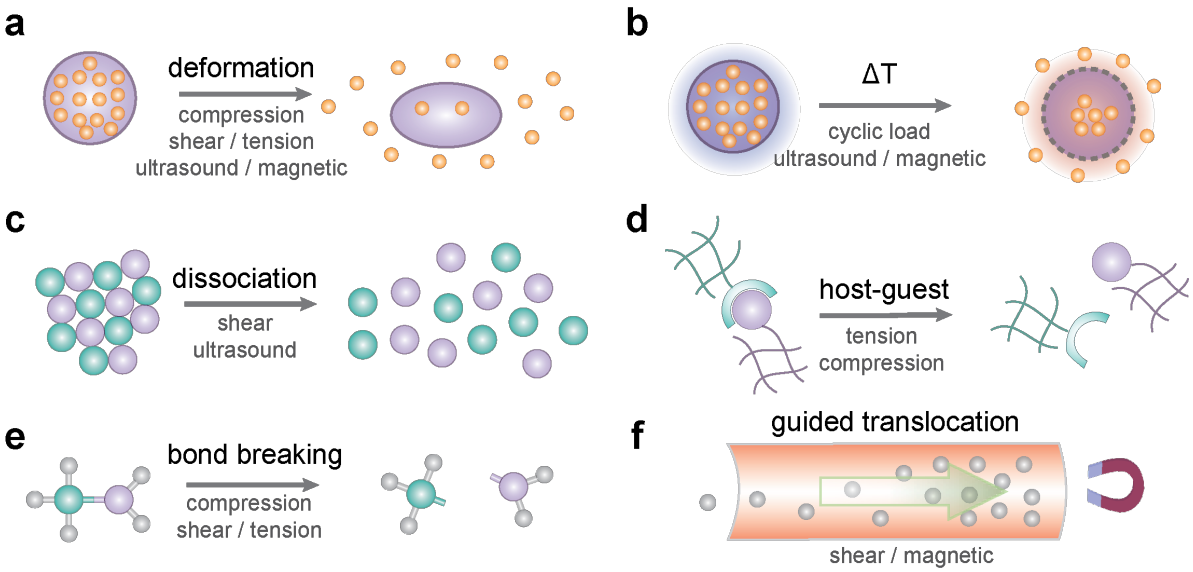

Figure 7. Diverse mechanistic activation in response to biomechanical stimuli. a) Biomechanical forces induced deformation and functionality execution. b) The coupling of thermo-responsiveness with mechano-responses. c) Mechanical forces triggered dissociation of assemblies with weak cohesion (*e.g.*, electrostatic attractions). d) Alterations in the host-guest interactions caused by mechanical forces. e) Bond breaking upon excessive mechanical forces. f) Guided accumulation of magneto-responsive and shear-responsive materials.

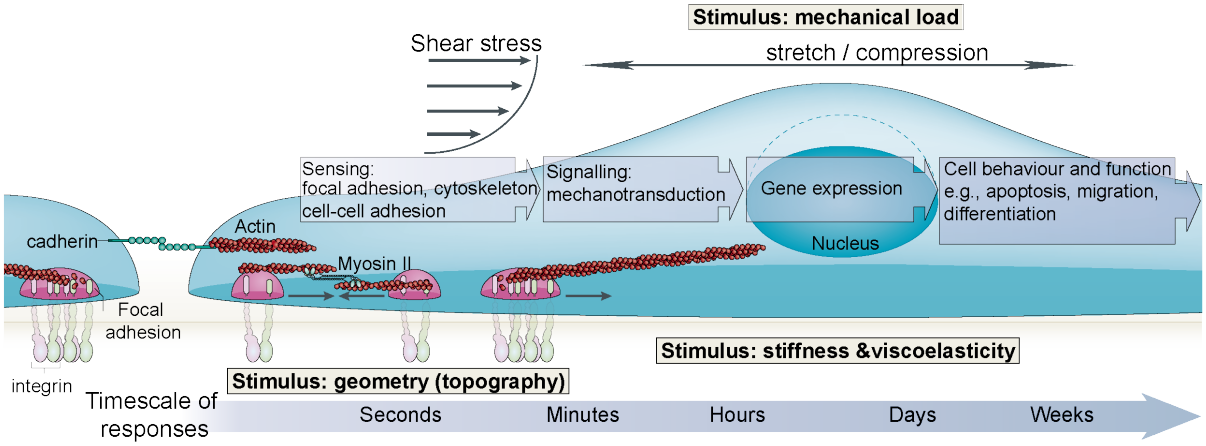

Figure 8. Cellular mechanotransduction enables biological responses to various mechanical stimuli, including geometrical constraints, stiffness and viscoelasticity, and mechanical load. Reproduced with permission.[15] Copyright 2014, Nature Publishing Group.

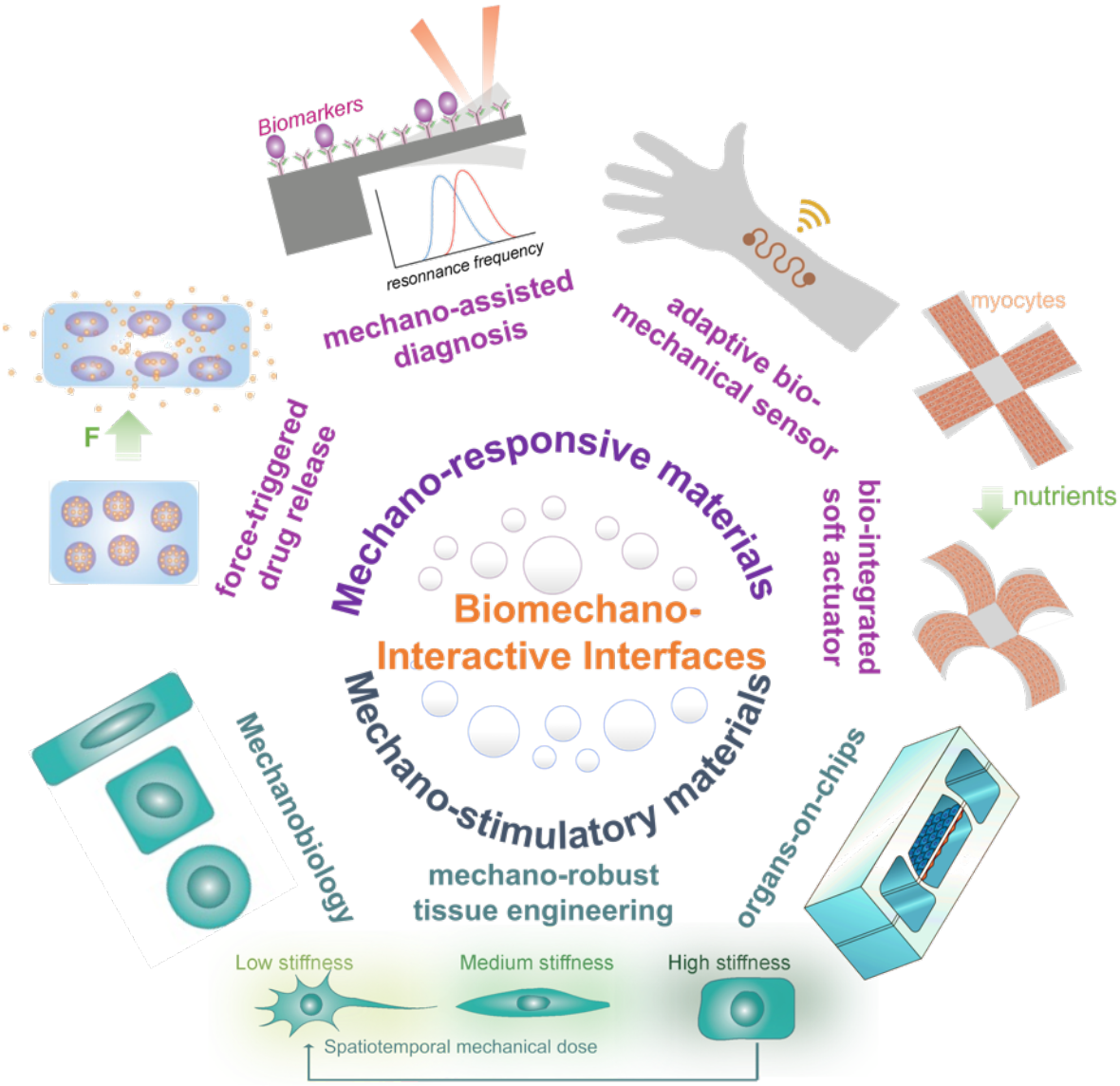

Figure 9. Implementations of biomechano-interactive materials and interfaces. Mechano-responsive materials are applied in adaptive biomechanical sensors, mechano-assisted diagnosis, force-triggered drug release, as well as bio-integrated soft actuator. Mechano-stimulatory materials are exploited in constructing mechanically robust scaffolds (geometry, stiffness, and viscoelasticity) for cell fate manipulation, and mechanical load for organs-on-chips.

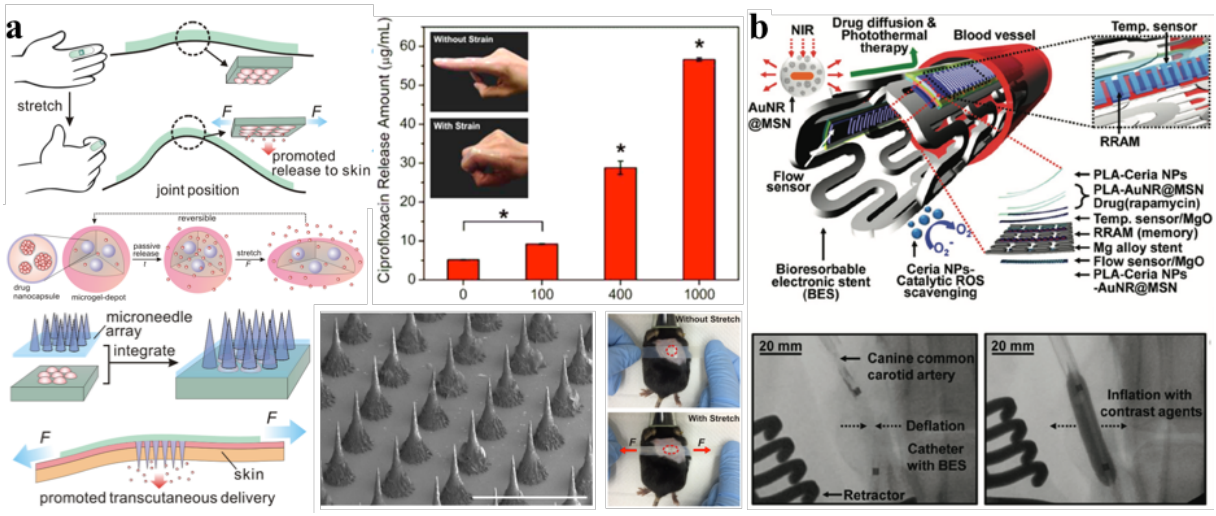

Figure 10. Force-triggered delivery of therapeutics. a) Schematic illustration of the smart delivery patch releasing drug upon stretch. The wearable device integrated with microneedle array (lower left) and SEM image of the microneedle array (lower middle). Scale bar: 1mm. Pictures showing the microneedle integrated device applied on dorsal skin of a mouse without (upper) or with strain (lower). Reproduced with permission.[32] Copyright 2015, American Chemical Society. b) Bioresorbable electronic stent embedded with therapeutic nanoparticles for endovascular disease treatment. Reproduced with permission.[48] Copyright 2015, American Chemical Society.

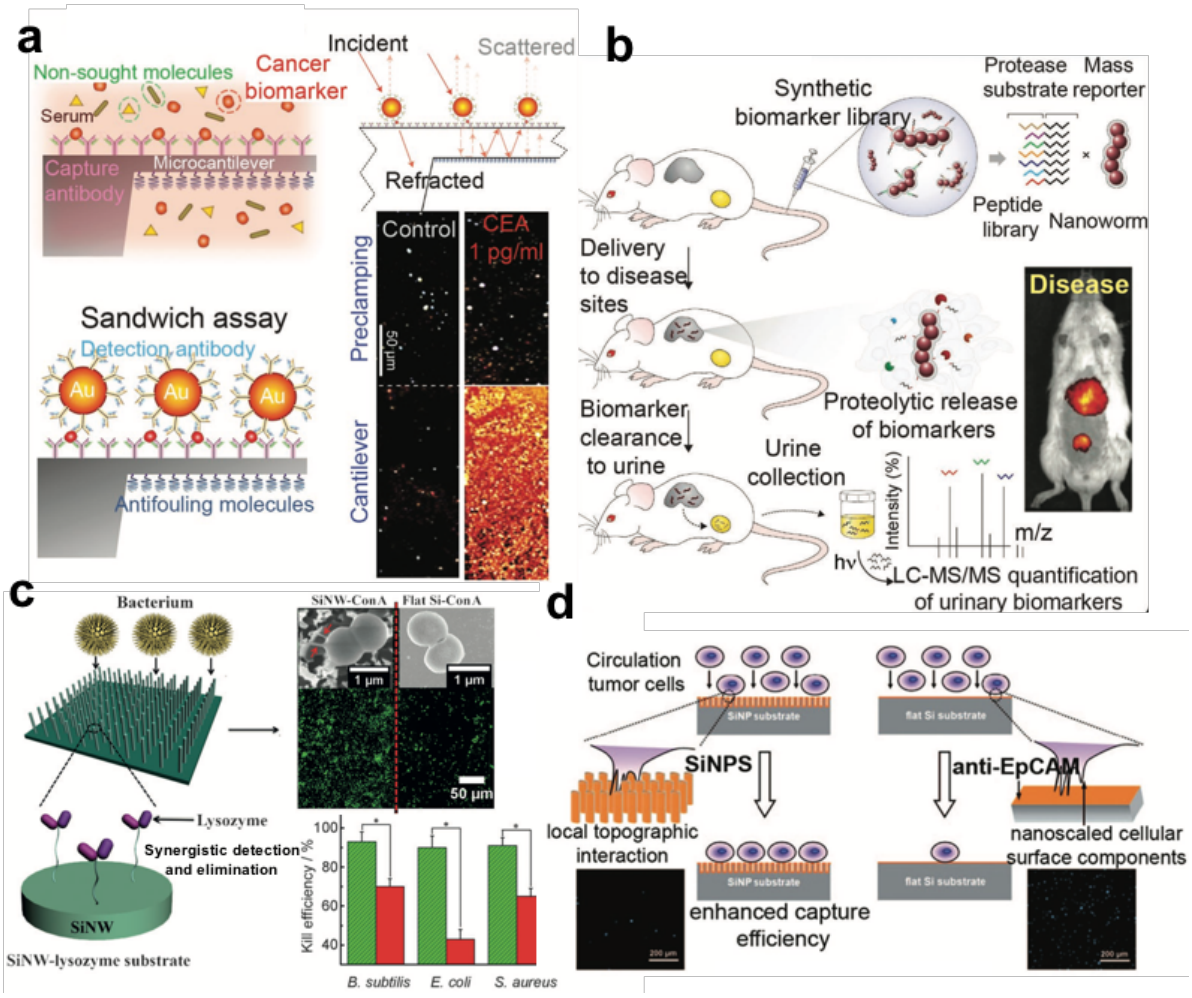

Figure 11. Mechano-assisted diagnosis. a). Ultrasensitive hybrid assay. Reproduced with permission.[111] Copyright 2014, Nature Publishing Group. b) Synthetic mass-encoded biomarkers made of NPs with conjugation to tandem peptides. Reproduced with permission.[112] Copyright 2013, Nature Publishing Group. c) Synergistic capture and elimination of ultralow bacteria enhanced by nanotopographical interactions. Reproduced with permission.[113] Copyright 2014, Wiley-VCH. d) Efficient detection of rare circulation tumour cells enabled by the interaction of local topographic geometry and nanoscale cellular surface components. Reproduced with permission.[114] Copyright 2009, Wiley-VCH.

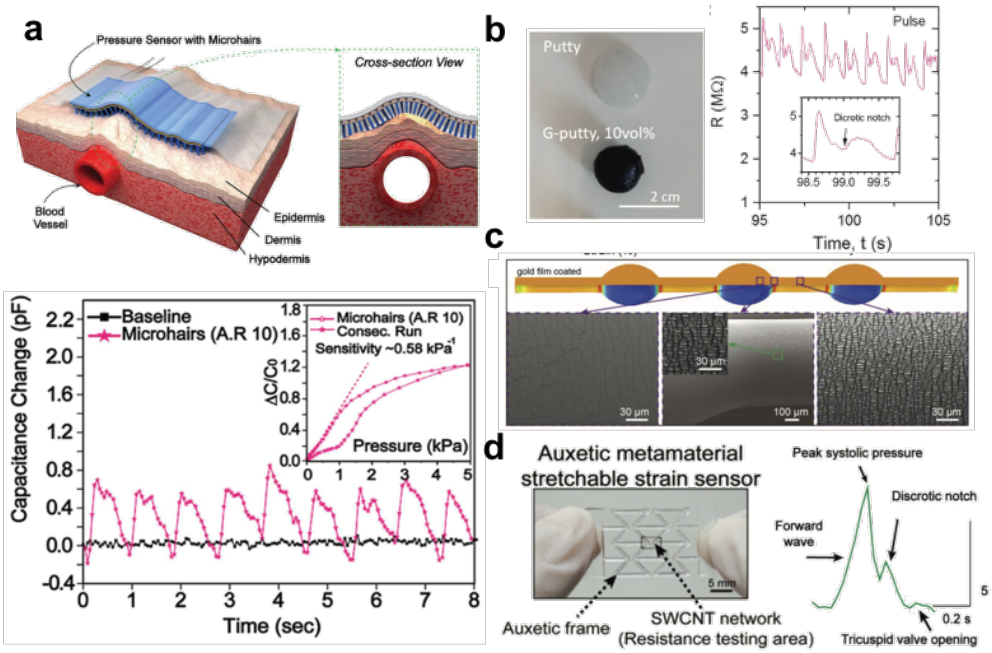

Figure 12. Ultrasensitive pressure and strain sensors for retrieving biophysical vitals. a) Highly skin-conformal capacitive pressure with bio-inspired microhairy interface. Reproduced with permission.[128] Copyright 2015, Wiley-VCH. b) An electromechanical sensor based on graphene-polysilicone nanocomposite (G-putty) for detecting breath and pulses. Reproduced with permission.[31] Copyright 2017, AAAS. c) Structural microfiber-shaped strain sensor with enhanced sensitivity via the redistribution of surface strain for motion detection. Reproduced with permission.[134] Copyright 2017, Wiley-VCH. d) Ultrasensitive strain sensors based on auxetic metamaterials for precise pulse recording. Reproduced with permission.[135] Copyright 2017, Wiley-VCH.

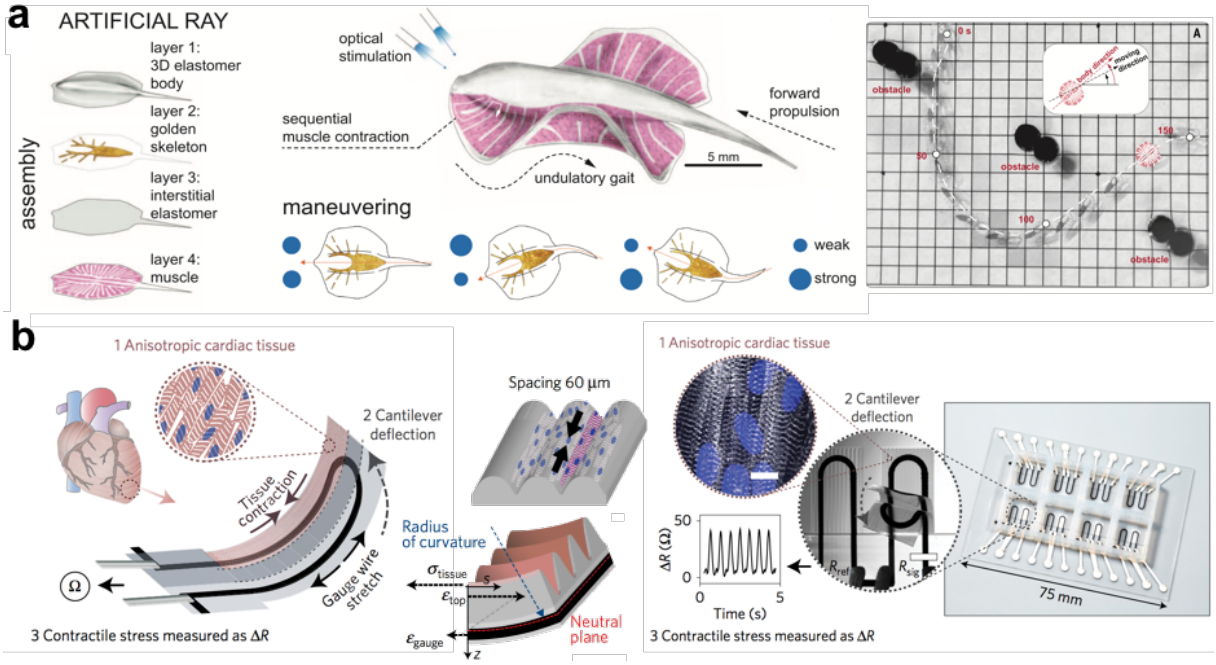

Figure 13. Bio-integrated soft actuators. a) A tissue-engineered ray swims and phototactically follows a light cue. Reproduced with permission.[34] Copyright 2016, AAAS. b) 3D printed cardiac microphysiological devices instrumented with strain sensor. Reproduced with permission.[42] Copyright 2016, Nature Publishing Group.

Table 2 Mechanical properties of selected tissues, natural ECM and synthetic matrices

Tissues, Natural ECM, Synthetic matrix		E (kPa)	$T_{1/2}$ (s)
Tissues/ Organs	Fat	0.02	100
	Brain	0.2-1.0	100
	Skin	4.5-8	-
	Lung	5	-
	Cardiac muscle	20-150	-
	Skeletal muscle	10-100	-
	Tendon	310,000	1
	Bone	11,500,000	-
Natural ECM	Collagen	0.01-6	1
	Fibrin	0.01-0.5	1
	rBM (Matrigel)	0.01-0.5	50
	Gelatin (covalently crosslinked)	0.6-13	-
	Hyaluronic acid hydrogel	4-95	-
Synthetic Matrix	Alginate hydrogel	0.1-110	44-3,300
	Agarose hydrogel	5-100	>1,000
	Polyacrylamide hydrogel	0.1-40	-
	Poly (ethylene glycol) hydrogel	0.1-160	-
	PDMS	5-100	-
	Polystyrene	3,000,000	-

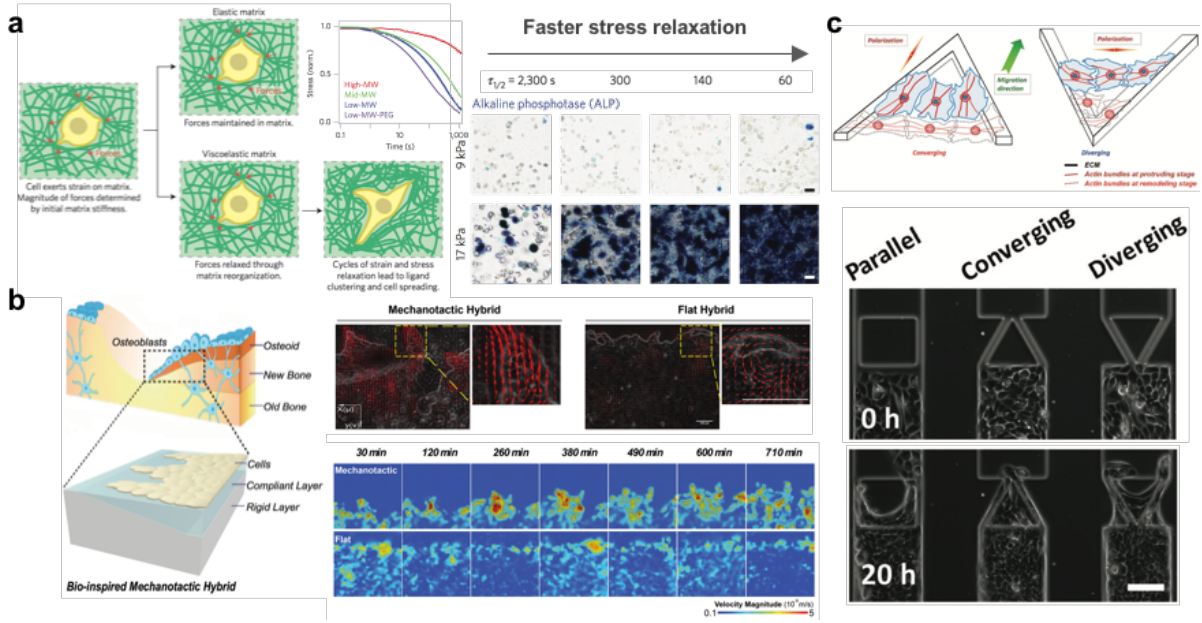

Figure 14. Effect of spatiotemporally dynamic mechanics on modulating cell physiology. a) The tunable viscoelasticity and stress relaxation properties of ionically crosslinked alginate, together with their initial elastic modulus, are capable of regulating differentiation of MSCs. Reproduced with permission.[149] Copyright 2015, Nature Publishing Group. b) The mechanotactic hybrids, comprising of the compliant and rigid layer with complementary gradient thickness, can drive the traction-mediated epithelial migration through the long rang intercellular forces transmission. Reproduced with permission.[86] Copyright 2016, Wiley-VCH. c) The epithelial closure regulated by the geometry of the underlying substrate through the orientational coupling of stress fiber with collective migration. Reproduced with permission.[78] Copyright 2017, Wiley-VCH.

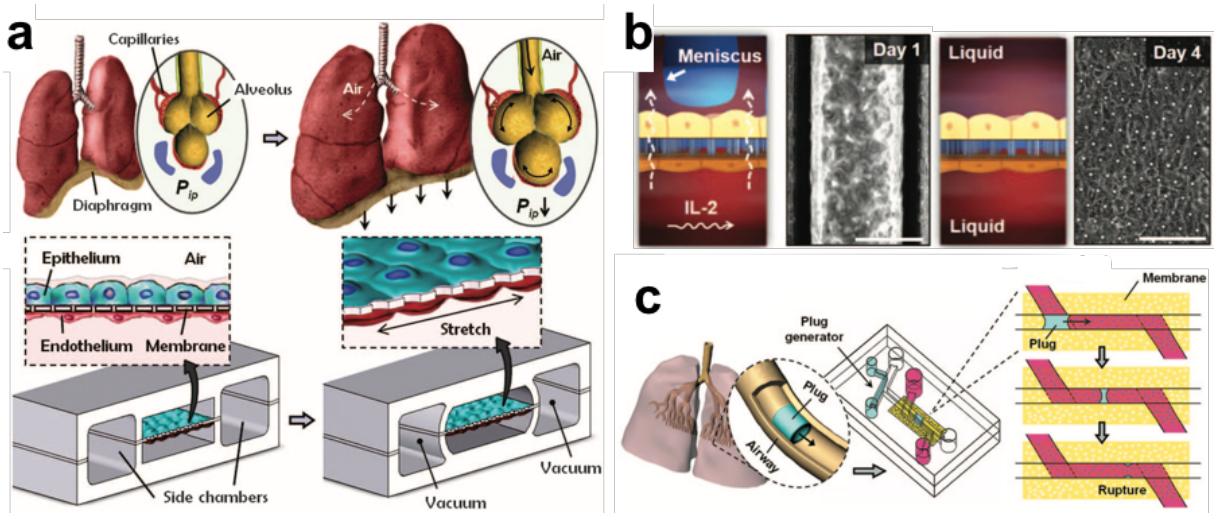

Figure 15. Mechanically-active lungs-on-chips. a) Reconstituted lung-on-a-chip revealing the role of cyclic stretching in organ-level immune responses to bacteria and nanoparticles exposure. Reproduced with permission.[41] Copyright 2010, AAAS. b) Organ-level disease model of anti-cancer drug toxicity-induced pulmonary edema. Reproduced with permission.[154] Copyright 2010, AAAS. c) Organ-level injury caused by deleterious fluid mechanical stresses of the liquid plug. Reproduced with permission.[155] Copyright 2007, National Academy of Sciences.

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Recent advances in biomechano-interactive interfaces have been employing the reciprocal mechanical interactions of engineered materials with biointerfaces, through the precise tailoring of the mechanistic activation of biomechano-responsive materials and the mechanical properties (stiffness, viscoelasticity and geometrical constraints) of biomechano-stimulatory materials, in a wide range of implementations, including mechano-triggered therapeutics and diagnosis, adaptive biophysical sensors, bio-integrated soft actuators, and mechano-robust tissue engineering.

Keyword: mechanoresponsive materials; tissue engineering; drug delivery; flexible devices; soft robotics

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Biomechano-Interactive Materials and Interfaces

ToC Figure