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Review Article

Mechanotransduction, nanotechnology, and nanomedicine

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Abstract

Mechanotransduction, a conversion of mechanical forces into biochemical signals, is essential for human development and physiology. It is observable at all levels ranging from the whole body, organs, tissues, organelles down to molecules. Dysregulation results in various diseases such as muscular dystrophies, hypertension-induced vascular and cardiac hypertrophy, altered bone repair and cell deaths. Since mechanotransduction occurs at nanoscale, nanosciences and applied nanotechnology are powerful for studying molecular mechanisms and pathways of mechanotransduction. Atomic force microscopy, magnetic and optical tweezers are commonly used for force measurement and manipulation at the single molecular level. Force is also used to control cells, topographically and mechanically by specific types of nano materials for tissue engineering. Mechanotransduction research will become increasingly important as a sub-discipline under nanomedicine. Here we review nanotechnology approaches using force measurements and manipulations at the molecular and cellular levels during mechanotransduction, which has been increasingly play important role in the advancement of nanomedicine.

Keywords: nanomedicine, mechanotransduction, mechanical force, differentiation, tissue engineering

Introduction

Mechanotransduction is the process by which organisms perceive physical forces by producing biochemical signals in response. Such signals have been shown to control cell proliferation, migration, differentiation, and death[1–8]. The significant influence of mechanotransduction on cells suggests potential clinical importance in modulating, altering, and controlling the process.

The recent discovery of the underlying molecular mechanisms of mechanotransduction advances the study closer to the point of clinical importance. Although mechanotransduction has been discovered for a long time and extensively studied at the cellular and tissue levels[9], it is just recently that its mechanism has been revealed at the single molecular level[4]. Although studies at cellular and tissue levels are still necessary to understand mechanotransduction, research on the process will increasingly apply nanotechnology. Clinical research into the applications of nanotechnology in mechanotransduction is becoming a sub-set of nanomedicine.

One of nanomedicine uses nanoparticles (NPs) for site-specific delivery of drugs and diagnostic agents. Some NPs show promise in helping to reveal the workings of mechanotransduction for tissue engineering, drug delivery, diagnostics, and other medical advancements.

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Mechanotransduction

Internal and external mechanical forces to the human body such as shear forces in blood vessels, stretching, actomyosin contraction, gravity, acoustic vibration, and pressure can regulate cellular development and various processes[4,10–15] (***Fig. 1***). For example, exposure to the microgravity environment of space travel reduces bone and muscle formation, and changes immune response and metabolism[25]. Mechanical niches of stem and cancer cells also regulate their fates such as differentiation and proliferation[26–27]. During aging, rigidity of human epithelial cells markedly increases, which also affects differentiation of their progenitor cells[28–29]. In these biological processes, DNA sequencing identified many expressed genes induced by the signals produced *via* mechanotransduction in response to mechanical inputs[30–31]. However, what is missing in mechanotransduction research is a complete understanding of how forces are sensed, transmitted, and transduced into gene expression. ***Fig. 2*** illustrates possible mechanotransduction pathways that have been partially revealed as described below. The major obstacle to reveal the molecular mechanism of mechanotransduction and its translation into gene expression is the difficulty in reconstitution of the reaction *in vitro*, where mechanical force is a difficult parameter to reproduce and disappears once biological samples are lysed. Despite the challenges, methods have been developed to unravel the molecular mechanisms of mechanotransduction.

Methods for studying mechanotransduction

To understand a biological system, scientists apply "input" into the system and read "output" as a standard approach. For mechanotransduction research, input is the mechanical forces applied to a cell or tissue (***Fig. 1***). Applying a controlled input of force can be achieved in several ways. For example, tissue culture cells can be repeatedly stretched on an elastic substrate in various directions and frequencies to mimic muscle, blood vessels, and lungs[36–38]. Hydrostatic pressure and membrane-stretching can activate channel proteins[39–40]. Cells can be compressed using a dynamic compressive bioreactor to engineer articular cartilage tissue and to mimic periodontal cells[41–43]. Shear stress can be generated by a pump to mimic blood flow[37,44]. Even microgravity can be tested on satellites and space stations, or in a rotating wall vessel bioreactor on the Earth[12,45–47]. Infrasound (0–20 Hz) and low-frequency noise (20–500 Hz) are also mechanical stimuli that influence physiology of cells and can be applied in research settings[48]. In addition to these external forces, internal forces can be controlled by inhibiting myosin. Stiffness of the substrate also affects the forces on adhesion molecules that link to the cytoskeleton and the nucleus[49–51].

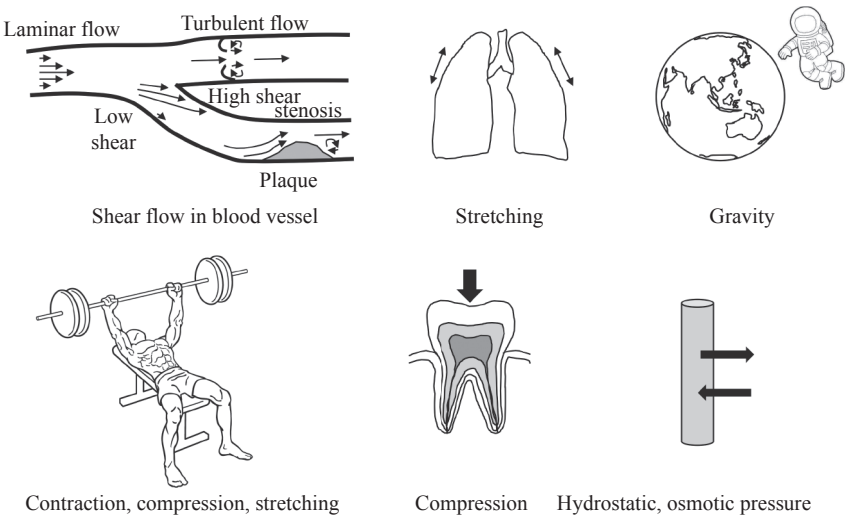

Fig. 1 **Mechanical forces influence human physiology and pathophysiology.** Shear flow in blood vessel influences physiology and pathophysiology of endothelial cells and blood cells (adapted from Nakamura *et al*[4]). Stretching of lung tissue regulates the synthesis of extracellular matrix[16–17]. Exposure to microgravity is associated with atrophy in heart, muscle, and bone, which is also frequented in aging[18–19]. Exercise-induced mechanical stimulus regulates gene expression for muscle fiber hypertrophy[20–21]. Application of mechanical stress on periodontal ligament fibroblasts induces gene expression to regulate the development, differentiation, and maintenance of periodontal tissues[22]. Hydrostatic or osmotic pressure promotes chondrogenesis of mesenchymal stem cells and the transition and differentiation of notochordal cells into nucleus pulposus cells in the intervertebral disc[23–24].

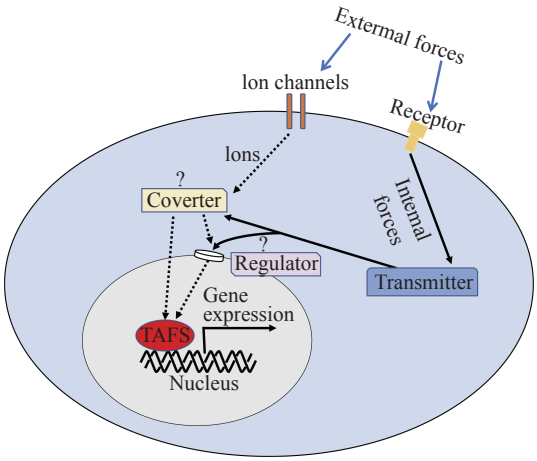

Fig. 2 **A schematic overview of how mechanical forces are converted to gene expression in a cell.** Some illustrated pathways were experimentally demonstrated. For example, external forces such as touching and stretching are sensed by mechanosensitive ion channels (*e.g.*, Piezo channels)[32]. Internal forces such as actomyosin contraction trigger mechanotransduction as well. Actin cytoskeleton mediates sensing and transmission of forces to regulate nuclear pore size, which controls localization of a trans-acting factor (red) such as Yes-associated protein 1 and megakaryoblastic leukemia 1[33–34]. Note that this diagram only depicts mechanotransduction pathways to gene expression. Mechanotransduction is also known to induce apoptosis, cell migration, and shape change[35].

"Output" in the experimental methods above includes gene expression, morphological changes, translocation of protein, and post-translational modification as these methods are well-established. However, as previously mentioned, these methods do not address how forces are sensed, transmitted, and transduced into gene expression, which have remained challenging questions in the field of mechano-transduction research.

How mechanical forces are detected

Accumulated evidence demonstrates that mechanical forces trigger conformational changes of proteins to activate them. For example, piezo cation channels use a lever-like mechanogating mechanism to function as a mechanotransduction channel[52]. Filamin A, an actin cross-linking protein, exposes a cryptic binding site for integrins and other binding partners when actomyosin contraction dissociates the domain-domain pair of filamin A[53–57]. Talin unfolding occurs in the R8 domain upon force application to activate downstream signaling[58]. Blood shear force can induce unfolding of the A2 domain of von Willebrand factor to expose the binding site for the glycoprotein Iα receptor in the A1 domain, cryptic A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) binding sites, and the cleavage site in the A2 domain[59–60]. Deflection of stereocilia of hair cells by acoustic forces pulls open a calcium channel and activates the current through the channel[61].

All of these demonstrations rely on detailed structural information as no robust method is available to identify a mechanosensing molecule. A nano-technology-based method that specifically recognizes mechanosensitive changes without recognizing non-mechanosensitive changes which could take place at the same time as mechanosensitive changes, is necessary to advance our knowledge of force sensing mechanisms. These changes could include not only conformational changes of protein but also other biological molecules such as membrane lipids and sugars.

How mechanical forces are transmitted

In theory, force transmission can be mediated by cell-matrix interaction, cell-to-cell interaction, cytoskeleton, pressure, and fluidic flow and vibration (***Fig. 2***)[62–64]. The cytoskeleton-mediated transmission is fast even across long distances compared to molecular diffusion in cells, presumably due to the direct connection of the sensor to a target[65]. However, in theory, pressure change, stretching, and vibration can also transmit faster than molecular diffusion. The cytoskeleton is directly connected to the linker of nucleoskeleton and cytoskeleton (LINC) complex to regulate gene expression[51,66–67]. In addition, osmotic shocks stretch the nucleus and nuclear pores to facilitate active transport of Yes-associated protein 1 (YAP), a transcriptional co-factor, into the nucleus[68].

The only means to identify a force transmitter is the perturbation of a candidate. For example, cytoskeleton can be perturbed by depolymerization agents such as latrunculin and nocodazole[69–70]. The LINC complex can be disrupted by targeting the component of the complex using siRNA and genome editing[68]. Another sophisticated method is necessary to identify and monitor force transmission at micro or nanoscales. For example, CRISPR screening may facilitate discovery of key mechanotransmitter and rationally designed fluorescent probe may monitor force transmission in real time[71].

How mechanical forces are converted to biochemical signals

The mechanotransduction channels can directly convert mechanical forces into biochemical signals by incorporating ions into cytosol[52,61] (***Fig. 2***). Upon

mechanical activation, filamin A can connect to integrin, smoothelin, and fimbacin, and dissociate FilGAP, a Rac-specific GTPase-activating protein[54–57]. The filamin A-integrin interaction regulates cell adhesion and migration, but functions of force-dependent interactions with smoothelin and fimbacin are not known[72]. Binding of FilGAP to filamin A targets FilGAP to sites of membrane protrusion, where it antagonizes Rac to control actin remodeling[73]. Mechanical forces also trigger proteolysis by exposing a cleavage site[59–60]. Enlargement of nuclear pore size regulated by mechanical forces such as substrate stiffness, indentation of plasma membrane by atomic force microscopy (AFM), and osmotic shocks enables the transport of YAP from cytosol to the nucleus to regulate gene expression[68,74]. Other means to convert mechanical forces into biochemical signals use actin polymerization that is triggered by mechanical forces by unknown mechanisms[75–79]. Polymerization of actin dissociates myocardin-related transcription factor A from unpolymerized actin in cytosol facilitates nuclear localization of mitochondrial transcription factor A to associate with several serum response factor target promoters[80–82].

Although several other molecules such as cadherin, catenin, and merlin are shown to be involved in mechanotransduction pathways, how mechanical forces are exactly converted to biochemical signals through these molecules are not known[83–86]. The major obstacle is the lack of nanoscale structural information before and after activation by mechanical forces.

Measurement of mechanical forces

Measurement of forces applied to tissue, cells, and eventually a single molecule is the basis of mechanotransduction research and application (***Fig. 3A*** and ***B***). However, reported values of cell stiffness and viscosity vary substantially depending on methods even when different groups use the same instruments (*e.g.*, elastic and viscous moduli of MCF-7 breast cancer cells can vary 1000-fold and 100-fold, respectively)[87]. Therefore, scientists need to be aware of the limitations of force measurement and confounding factors such as heat introduced by probes. Unfolding forces of protein domains such as fibronectin type Ⅲ and immunoglobulin domains also vary depending on methods due to different loading forces, loading rate, and other factors[88–91]. AFM measures the forces required to unfold individual domains of titin, ranging from 150 to 300 pN, whereas magnetic tweezers detected the critical force (~5.4 pN) at which unfolding and folding have equal probability[90,92]. This is the case for unfolding of filamin immunoglobulin domains too. The unfolding force ranged from 50 to 220 pN by AFM, whereas magnetic tweezers revealed two different modes of unfolding at <10 pN and >20 pN[88,93]. The difference

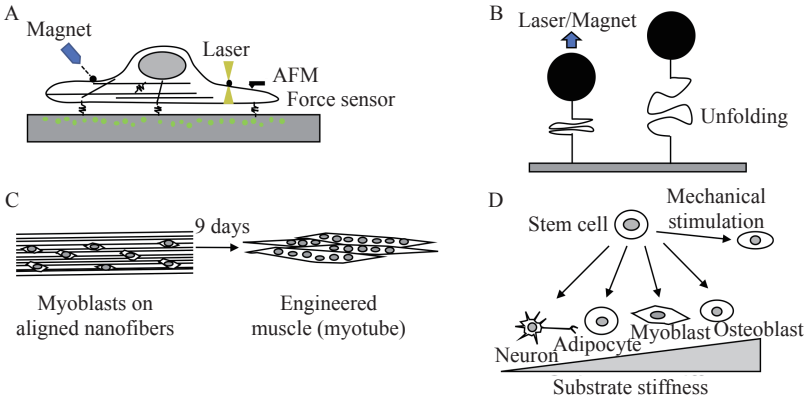

Fig. 3 **Application of nanotechnology on mechanotransduction research.** A: Measurement of mechanics and mechanical forces of a living cell. Magnetic tweezers and optical tweezers measure mechanics of a cell using a magnetic bead and microscopic objects coated with specific ligand that attaches to cell surface receptor. Atomic forcemicroscopy (AFM) measures cell mechanics by directly touching a cell. Force sensor fused into adhesion molecule or attached on substrate measure traction force of a cell. Traction force microscopy measures displacement of microbeads embedded in the substrate to determine traction force. Other methods, not shown in this figure, include micropillar array to detect traction force and fluorescent resonance energy transfer (FRET)-based probe to map stress within a cell. B: Measurement of mechanical properties of a single molecule using magnetic and optical tweezers. AFM can be used for a single molecular analysis but loading rate is much higher than that used in the magnetic and optical tweezers. Fusing an internal control molecule whose mechanical property is known to a test molecule can be used to warrant single molecular analysis. C: Pattern of nanoscale scaffold regulates cell behaviors. D: Stiffness of nanoscale scaffold and mechanical stimulation regulate cell differentiation. For example, nanoparticles can be mechanically manipulated to activate a specific signaling pathway to induce differentiation, growth, and death.

between AFM and the magnetic tweezers is that the loading rate of the magnetic tweezers is much lower than that used in the AFM experiments[93–94]. Although the magnetic tweezers is a choice to measure physical property of biological molecule in physiological condition, AFM can be used to characterize molecule under high-force pulling and to determine molecular-molecular interaction.

The optical tweezers demonstrated that application of 2–5 pN to filamin domain increases the affinity to its binding partners[95]. The computational calculation of the critical force required to denature an immunoglobulin domain is calculated to be 3.5–5 pN using the energy difference between the folded and unraveled domain[96]. Since the forces generated by single myosin or kinesin molecules are 2- to 7-pN force, single and multiple motor molecules are capable of unfolding an immunoglobulin domain[97–98].

Nanoscale molecular sensors can also measure mechanical forces loaded on a single molecule in living cells. Fluorescent resonance energy transfer (FRET)-based probes can be genetically constructed and expressed in living cells. Since FRET changes correlate with forces, force can be measured in the cells. For example, a vinculin probe demonstrated that tension across vinculin in stable focal adhesion is about 2.5 pN and changes as cells migrate[99]. In talin, the rod domain experiences a force gradient (in the single piconewton regime) upon integrin-mediated cell adhesion[100], which is consistent with single molecular analysis[101]. At cell-cell junctions, it was estimated that cadherin-catenin complex is subjected to a tension of ~5 pN under resting conditions rising to ~50 pN in stressed conditions consistent with experimental measurement[102]. FRET-based tension sensors can be used to determine traction forces at the cell surface that attaches to substrate as well[103]. Recently developed nanofiber optic force transducers have the potential to measure intracellular forces with sub-piconewton force sensitivity and a nanoscale footprint[104].

Manipulation of mechanical forces

Nanotechnology is powerful to mechanically manipulate conformational changes of a molecule. For example, magnetic NP is a promising technique for activating a specific signaling pathway, controlling stem-cell differentiation, inducing cancer-cell death, and treating nervous system diseases[105–107]. The NPs can be made in customized sizes and surface characteristics with a high surface to volume ratio, and can be ingested by cells. Magnetic micropillar substrate can also be used for mechanotransduction research and application[108]. Optical and magnetic tweezers that control from nano- to 2–3 micron-particles can be attached to specific position of a molecule through linkers and internal control such as antibody and green fluorescent protein[109–111]. AFM allows a single molecule to be imaged but also to be manipulated using a cantilever tip[112–113]. Furthermore, high-speed AFM has recently been developed to record dynamic action of biological molecules (currently at 10–16 frames/s)[114]. These techniques can be applied to mechanically stimulate cells[68,115–116].

Application of mechanotransduction research in nanomedicine

Although mechanotransduction is essential during development and repair of tissues, the difficulty of mimicking the natural properties of tissues is one of the bottlenecks in applying mechanotransduction research to tissue engineering. Nanotechnology through customized nanomaterials has the potential to solve this problem. For example, stem cells can be differentiated into different types of cells by manipulating substrate rigidity and topography[117–119] (***Fig. 3C*** and ***D***). More specifically, a defined substrate topography induces chondrogenesis and osteogenesis from human mesenchymal stem cells[120–123]. Culturing myoblasts on aligned nanofibers engineer muscle (myotube) that can be used for skeletal muscle repair and generation[124]. Moreover, reduced graphene oxide, a low-weight 3D aerogel-like material with pore diameter in the range of approximately 5 –10 μm, induces neuronal differentiation of human neuroblastoma cells by modulating RhoA/Hippo pathway[125]. Doping NPs into hydrogel improves the scaffold mechanics for tissue engineering such as treatment of myocardial infarction and skin scar, bone regeneration, proliferation and differentiation of bone marrow and periodontal stem cells[126–130]. These results suggest that nanotechnology can be used to manipulate matrix and tissue mechanics to control cell fate to repair and generate tissues. In this aspect, an organoid, a simplified and miniaturized version of an organ produced *in vitro* in 3D, can be a good model to study application of mechanotransduction regulated by nanotechnology[131–132].

Although NP-based diagnosis and therapy are the major topics of nanomedicine, it was recently demonstrated that cellular uptake of NPs are cell mechanics dependent[133]. Since mechanical properties

of normal and diseased cells are significantly different[134], these results suggest the application of mechanotargeting of NPs in nanomedicine[135]. Moreover, the success of a shear-activated drug-delivery system inspired by platelet activation suggests that such a system can be applicable to perturb a specific mechanotransduction pathway[136].

Magnetic NP is a promising tool to remotely activate mechanotransduction. For example, mechanical activation of force-sensitive TWIK related potassium (TREK1 K^+) channel and integrin using magnetic NPs promotes mineralization of bones[137]. The magnetic NPs can also remotely control brain circuits[138].

Other nanomaterials possessing particular physical and chemical properties, such as carbon nanotubes and nanofibers can be used for tissue engineering. These materials are biocompatible, stable, easy to fabricate and functionalize, and have a potential effect on neurogenesis, osteogenesis, and stem cell differentiation due to their mechanical properties related to mechanotransduction[123].

Although application of nanotechnology in mechanotransduction research and tissue engineering is already beginning to happen and show promising results, safety of nanomaterial should be vigorously tested before medical application[139–140].

Conclusion and future perspectives

Mechanical forces have a profound effect on human physiology and pathophysiology. Although research on tissue and cellular level is still necessary to understand mechanotransduction, its molecular mechanism at nano level should eventually be revealed for the potential of clinically significant findings. Nanotechnology provides a new set of tools for studying mechanotransduction and for its application in nanomedicine. Such nanomedicine includes force-induced therapeutics, diagnosis, and tissue engineering, which will offer unprecedented opportunities for innovative medicine. However, an understanding of mechanotransduction at the molecular level is still nascent, retaining its application in nanomedicine. Of critical importance is the need to identify a full-set of mechanosensing molecules and reveal how forces are sensed, transmitted, and converted to biochemical signals and gene expression. Such understanding should lead to the development of more selective drugs and treatment.

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