In this R&D area, the main objective is to understand the body’s systems for sensing, transduction, and response to physical stimuli and to create platform technologies with healthcare applications. When the cells making up the body are exposed to different physical stimuli, such as skeletal muscle/organ functioning, blood flow, gravity, or signals originating from neighboring cells and substrates, they use these stimuli to self-regulate replication, differentiation, death, morphogenesis, or movement. We do not yet have a detailed understanding of how the cells perceive physical stimuli or how these stimuli elicit physiological or pathological responses after the stimuli have been converted into intracellular signals. Mechanobiology is a new R&D area that combines physics, engineering, medical science, and biology to investigate such questions and clarify the role of physical stimuli in regulating the structure and function of cells, tissues, organs, and the body as a whole. A better understanding of the mechanisms involved in perception of and response to physical stimuli is expected to open up new avenues of research in the quest to understand currently unresolved issues like how the body develops, grows, and forms tissues; how a failure of these mechanisms leads to disease; or how to develop regenerative medicine techniques for tissues and organs. We also expect to develop devices that can quantitatively apply and control physical stimuli or platform technologies for the precise measurement of biological responses to physical stimuli.
We will uncover the molecular mechanisms that transduce mechanical stimuli from cytoplasm to nucleus in living organs and tissues to control gene expression profiles. Based upon our findings, we will develop novel techniques to manipulate cells mechanically in a macroscale level. In addition, we will discover new therapeutic ways, namely, exercise mimetics and exercise pill, to combat with diseases, such as metabolic syndrome, disuse atrophy and cardiovascular diseases.

Mesenchymal stem cells (MSCs), one of the most useful cell sources for regenerative medicine in these days, tend to deteriorate its stemness depending on the mechanical conditions of culture substrate. Therefore, special cares are required to maintain its quality from the view of stem cell mechanobiology. For this issue, we have fabricated microelastically-patterned hydgel, applied it for MSC culture, and discovered a phenomenon of “frustrated differentiation” which enables to inhibit lineage specification of MSCs. In this project, we elucidate the mechanism of the frustrated differentiation as well as development of the culture substrate that ensures to keep high quality stemness of MSCs.

The weight-bearing exercises help to build bones and to maintain their strength. On the other hand, bone loss with bedridden and space flight are well known as essential problems. Bone is constantly renewed by the balanced action of osteoblastic bone formation and osteoclastic bone resorption both of which mainly occur at the bone surface. This restructuring process called “bone remodeling” is important not only for normal bone mass and strength, but also for mineral homeostasis. However, the molecular basis for the regulatory mechanisms underlying bone remodeling in response to mechanical stimuli has not been sufficiently elucidated. Based on this novel concept of a regulatory mechanisms mediated by osteocytes in response to mechanical stimuli (the “ostemechano-cascade”), we plan to investigate the biological systems of osteocytes through approach combined with comprehensive analysis and sophisticated genetically modified mouse system.

Hearing is essential for human life. This sensation is triggered by transduction of nano-scale vibrations induced by acoustic stimuli to electrical signals in the ‘cochlea’ of the inner ear. Deafness, which afflicts 10% of the global population, emerges primarily from disruption of the cochlea; the causes of this disease remain largely uncertain. In this study, we will focus highly sensitive and tuned mechanical response of the cochlea and investigate the underlying mechanisms and their pathological significance by interdisciplinary approaches. Furthermore, on the basis of the results we will develop a next-generation device to assist hearing for patients with deafness.

As one of the mechanotransduction pathways that convert mechanical stimuli into biochemical activities, it is recently suggested that load applied to a tissue may deform cells in the tissue, causing the deformation of their nuclei, and nuclear deformation may affect the distribution of chromatin, and finally stimulate mRNA transcription. In this project, we take artery walls as the test model, and aim to study in detail and quantitatively how the deformation applied to artery wall is transferred to cells, then nuclei, and finally chromatin, and how the change in chromatin distribution causes mRNA transcription by combining multi-scale experiments and computer simulations.
We study mechanobiology dealing with mechanical phenomena in the human body, especially focusing on cellular sensing and mechanotransduction mechanisms underlying the responses to mechanical stimuli. The main theme of our study is to elucidate how vascular endothelial cells sense hemodynamic forces (i.e., shear stress and stretch) generated by blood flow and blood pressure. This would be of benefit not only for understanding the blood flow-mediated regulation of vascular functions, angiogenesis and vascular remodeling, but also for the elucidation of clinically important problems, such as the development of cerebral aneurysms and atherosclerosis.

Tendons and ligaments are tissues that exert their functions by linking muscles and bones accurately and tightly, and their disorders and diseases cause the patient to dramatically lower daily life. In this study, we will examine molecular mechanisms of tendons/ligaments development and homeostasis via a mechano signal cascade and apply the finding to tendon regenerative medicine.

Sugar chain is an important biomolecule that coordinates cellular membrane environment. Changes in its quality or quantity affect mechanical response in muscle cells, sometimes leading to human diseases. In this study, we will investigate membrane molecular environment essential for appropriate mechano-sensing/response that includes sugar chains and proteins either directly or indirectly interacting with mechano-sensor proteins. We will also clarify mechanism how muscle cells maintain the cellular homeostasis utilizing mechanical stress and the pathogenesis associated with disrupted mechano-sensing/response. Finally, we will develop therapeutic strategies for mechano-fragile muscular dystrophy/muscle atrophy or mechano-adaptive myalgia.

Abnormally stiff substrates have been shown to trigger cancer progression. Our main goal in this research and development program is to elucidate the detailed molecular mechanisms underlying this trigger. We focus on the influence of cancer-associated fibroblasts (CAFs) on the progression of cancer. Moreover, we examine the involvement of lipid rafts regulated by the stiffness of the extracellular matrix in cancer cell migration. We are also developing a new screening system to observe the effects of substrate stiffness on malignancy, aiming to find a possible therapeutic target for tissue stiffening causing cancer.

Skeletal muscle has the ability to respond to mechanical stress, suggesting that skeletal muscle has mechanosensor that sense and convert mechanical signals into biochemical signals. However the details of those sensors or signals remain unclear. Recently it has been reported that mitochondrial dysfunction causes various diseases including muscle atrophy. In addition, mitochondria have been demonstrated to activate several intracellular signaling pathways upon mechanical stress. Therefore, we hypothesize that mitochondria can feel and respond to mechanical stress as mechanosensors, and that mitochondrial responses against the excess or deficiency of mechanical stress may collapse skeletal muscle homeostasis. In this project, we try to verify our hypothesis and to investigate the mitochondrial signaling pathways that regulate skeletal muscle atrophy or hypertrophy.
Neurons extend axons and form elaborate networks in the brain. In this study, we will elucidate the molecular mechanics underlying cell migration and axon guidance (chemotaxis + haptotaxis + durotaxis), and formulate a mathematical model to describe them. This study also analyzes a mechanosensor system responsible for axonal haptotaxis. In addition, we will elucidate the molecular pathology of L1-CAM syndrome, with characteristic symptoms corpus callosum hypoplasia, mental retardation, dysphasia, spastic paraplegia and hydrocephalus, and the molecular mechanisms of malignant glioma cell invasion. We also analyze the molecular mechanics underlying dendritic spine formation, by expanding the model of axon guidance.

The main aim of this research is to elucidate the mechanism of acceleration of wound healing by compression force applied by our original non-contact airborne ultrasound device. Cyclic compression by our device accelerated wound healing in mice models. This accelerated healing was accompanied by the increased epithelization and the granulation tissue formation facilitating contraction of the collagen matrix and wound closure. We also focus on activation of Notch signaling pathway and high-frequency calcium oscillation of human microvascular endothelial cells which have been compressed from the apical surface. We expect to construct a fundamental technology of mechanotherapy using the ultrasound device.

Heart failure is a leading cause of death worldwide. It has been thought that disruption of cardiac response to mechanical stress is essential for heart failure, but the central molecular mechanisms remain elusive and there is no effective treatment targeting the pathogenesis. In this study, we focus on cardiomyocyte mechanosignaling molecules to elucidate the nature of heart failure. This study would lead to the comprehensive understanding of pathogenesis of heart failure and the development of novel therapeutic approaches.
We have previously reported that TRP vanilloid family type 2 channels (TRPV2) can be activated by hypotonicity- and stretch-induced mechanical stimulation. In this project, we aimed to understand the roles of TRPV2 in mechanical-signal-dependent remodeling of physiological function and structure in a wide variety of tissues using several types of tissue-specific TRPV2 knockout (KO) mice. We also clarify the mechano-feedback mechanisms required for the maintenance of cellular structure and function in several tissues. These studies will elucidate the molecular bases of mechanotransduction and their physiological role for maintaining homeostasis. In addition, we will propose the effective therapeutic targets for the diseases caused by defects in mechano-feedback signal transmitted via TRPV2.

Proper mechanical loading is essential for maintenance of bone and cartilage, meanwhile exposure of articular cartilage to excessive mechanical loading is deeply involved in the pathogenesis of osteoarthritis. In this project, we examine molecular mechanisms underlying cartilage anabolism by proper mechanical loading and cartilage degeneration by excessive mechanical loading. We further aim to develop novel therapeutics by applying the findings of chondrocyte mechanoresponses.
Elucidating the mechanisms of mechanotransduction in angiogenesis

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Angiogenesis, the growth of new blood vessels from pre-existing vessels, plays an important role not only in regulating physiological functions but also in development and progression of various diseases. In this research project, we try to elucidate the mechanisms of mechanotransduction in angiogenesis to develop effective vascular regeneration therapy for ischemic diseases and novel treatment of pathological angiogenesis-related diseases. To this end, we investigate the following two issues by performing fluorescence-based bioimaging using zebrafish as a model animal: (1) the molecular mechanisms by which mechanotransduction mediated by cell adhesion apparatus regulates endothelial cell dynamics during angiogenesis and (2) the regulatory mechanisms of angiogenesis by mechanical stresses such as shear stress and intravascular pressure.

Non-invasive force measurement using fluctuation for organelle transport in neurons

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Organelles are transported by motor proteins, as if cargos are carried by couriers. Because of this transport, substances necessary for life activity spread everywhere in a cell. We develop a non-invasive force measurement method using fluctuation in the motion of an organelle observed by fluorescence microscopy. Using the method, we investigate the role of motor proteins on axonal transport and neuronal diseases caused by the deficit of the transport.

Development of biomimetic microdevices to recapitulate physiological mechanical stimulation to model hematopoietic function

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This study aims to develop a novel in vitro platform to simulate hematopoietic function by recapitulating physiological microenvironment using microengineering techniques. We reconstitute embryonic endothelium to generate hematopoietic stem cells (HSCs) from induced pluripotent stem (iPS) cells by recapitulating the mechanical microenvironment. Since HSCs arise at arterial sites of the embryonic vasculature after the initiation of heartbeat, mechanical forces based on heartbeat are linked to hematopoietic development. By controlling mechanical microenvironment, we try to understand mechanobiology of hematopoietic development and blood physiology. Our goal is to model hematopoietic function in vitro using the biomimetic microdevices with iPS-derived cells.

Elucidation of plasma membrane tension dependent signal transduction in cancer cell invasion and metastasis

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Recent advanced biophysical techniques have found that while tumors are stiffer than normal tissue, malignant cells themselves are much softer than their normal counterparts. However, molecular mechanisms by which cell stiffness controls cancer cell invasion and metastasis are largely unclear. In this project, I focus on the mechanical tension of the plasma membrane (PM) and membrane-bending BAR proteins, and attempt to reveal how PM tension dependent signaling pathways govern cancer cell invasion and metastasis. I also explore whether breast cancer metastasis could be prevented by the manipulation of PM tension or by genetic targeting of membrane-bending proteins.
Heart is a unique organ which is under the control of mechanical stress for 24 hours per day and 7 days per week. Therefore, in the heart sensing system against mechanical stimuli, mechano-sensor, is extremely important. We recently found that pannexin, a family of gap-junction channel, is one of the mechano-sensor in the heart. In response not only to mechanical stress but also to ischemic stress activates pannexin and induces the release of ATP. ATP-release provides the protection against mechanical and ischemic stresses. Our aims are to clarify the underlying mechanism of pannexin-mediated protection, and to search low-molecular chemicals activating pannexin.

Although all cells in a multicellular organism contain the same genome in DNA, they look different and perform different functions. The difference is caused by the difference in gene expression pattern occurring during differentiation. This study aims to clarify the mechanism how mechanical and structural properties of the microenvironment where the cells reside affect the intracellular mechanical forces transmitted to DNA, and further modulate cell fate determination and differentiation. The finding will be a basis to develop tissue engineering that creates various tissues and organs by utilizing mechanical and structural cues provided by the artificial microenvironments.

The motility of cilia and flagella including transport of body fluid, mucous, and signaling molecules has an essential role in the maintenance of life. This project aims at unveiling the mechanical feedback system in cilia and flagella such as an increase or reversal in the motility upon rise in mechanical load. The obtained outcome would help to unravel ciliopathy and to develop drugs acting on the factors regulating the motility of cilia and flagella.

In this project, I’m aiming to reveal cellular memory phenomena in response to environmental mechanostuctural factors, such as topography and elasticity of substrates, and its mechanism. Specifically, I will develop a dynamic cell culture platform enabling spatiotemporal control of substrate topography and elasticity in order to investigate the effect of the culture history of an extracellular mechanostuctural environment on stem cell behaviors. Understanding the spatiotemporal role of mechanostuctural information of cellular surrounding through this project leads to further an emergence of dynamic mechanobiology research.

The cells constituting our bodies sense and respond to various mechanical forces. The mechanoresponses are crucial for many important physiological processes including the maintenance of homeostasis in body and morphogenesis in development. In this study, we focus on cytoskeletal reorganization in response to mechanical stimuli, and search for mechanosensory proteins and investigate the molecular mechanisms of sensing of mechanical stresses and the intracellular processes of mechanotranduction. The findings of our research will contribute to elucidate the pathogenic mechanisms of cardiovascular diseases and cancers caused by abnormalities in these molecular mechanisms.
In morphogenesis, each organ in our bodies acquires appropriate shape and composition of cell types to function properly. In this project, by using Drosophila genetics and imaging techniques, I am trying to uncover molecular and cellular mechanisms that ensure the robustness of organogenesis. Especially, I am focusing on mechano-sensing mechanisms by which cells adjust their gene expression to the change of epithelial tissue architecture during epithelial morphogenesis. In the end, I aim at uncovering the novel mechano-feedback system to harmonize tissue architecture with cell differentiation precisely at molecular levels.

Intracellular and extracellular mechanical forces affect the dynamics of actin cytoskeleton, however, the underlying biophysical mechanisms how forces are transduced into changes in the actin dynamics remain largely unknown. We propose a new hypothesis that actin filaments work as a tension sensor and will explore the mechanism behind the tension sensing.

The renal glomerular podocytes line the outer aspect of the glomerular capillary tufts, and are involved in the production of primary urine. Podocytes have numerous cellular processes, undergo dynamic morphological and functional changes, and are impaired by excessive mechanical stress in diabetes and hypertension, causing proteinuria and glomerulosclerosis. In this project, we aim to investigate the molecular mechanisms of mechanosensing, mechanotransduction, and mechanoresponse in podocytes, focusing on Rho family small GTPases and actin cytoskeleton in in vitro and in vivo systems. We also aim to develop innovative evaluation method of intraglomerular pressure by searching for markers reflecting glomerular pressure.

Myoblast fusion and subsequent elongation of multinucleated syncyia are fundamental steps to generate myotubes, the precursor of muscle fibers. Membrane tension is known to be crucial for myogenesis, but the underlying mechanisms remain to be elucidated. The aim of this project is to investigate the role of phospholipids, the components of lipid bilayers, in myotube formation. Especially, we are interested in the functional interplay between membrane-resident mechanosensing machineries and phospholipid flippases that catalyze translocation of phospholipids from the outer to the inner leaflets of the membrane. Our project may provide insights into therapeutic strategies for muscle disease.

Osmolality and Na⁺ level in body fluids are maintained within a specific physiological range. Dehydration causes an increase in body-fluid osmolality and Na⁺ level, which is detected by some brain sensor molecules, leading to the generation of thirst and suppression of salt-appetite. Information about the Na⁺ level in body fluids is also used by the body for blood pressure control. The purpose of this research project will be identify the molecular entity of the brain sensors involved in body-fluid homeostasis and blood-pressure control and to reveal the mechanism and physiology of the regulatory mechanism based on the information from the brain sensors.
Quantification of stress/deformation/signal fields and data assimilation to understand and predict mechanics of a growing epithelial tissue

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How do cells push and pull each other to trigger precisely the deformations of a tissue when shaping the body? The answer to this fundamental question is crucial for understanding the development of animal forms including our body. Over the next 3 years, we propose to extend our earlier research work and elucidate how tissue mechanics and biochemical signaling are orchestrated to control epithelial tissue morphogenesis. Specifically, by combining fly genetics, live imaging, quantitative data analysis, physical modeling, and data assimilation, we aim at understanding the emergence of different tissue shapes regulated by the multi-scale feedback mechanism.
Elucidation of invasion mechanism of glioma stem cell-derived population response induced by interstitial flow

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Elucidation of an invasion process of glioma, which is a brain tumor, is an urgent issue for the treatment of glioma. In this project, we recapitulate tumor microenvironments using a microfluidic device, and investigate an invasion mechanism of glioma stem cells (GSCs), which respond to the application of interstitial flow. In particular, we focus on the mechanism how GSCs respond to the flow and recognize surrounding environments, which may contribute to the development of a future therapeutic strategy as well as diagnostic devices.

Identifying and manipulating molecules responsible for insufficient transcriptional activation of HSF1 and mitochondrial adaptabilities in aged skeletal muscle

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We have reported that heat stress improves mitochondrial function in skeletal muscle. Mitochondrial dysfunction with age in skeletal muscle leads to sarcopenia, which causes systemic age-associated diseases. Hence, improving mitochondrial homeostasis in skeletal muscle by heat therapy can contribute to the extension of health span. Unfortunately, even if heat therapy was given to aged mice, the magnitude of mitochondrial adaptabilities was approximately 50% or less as compared with young mice. To establish an innovative heat therapy to extend health span in the elderly, the proposer will elucidate molecular mechanisms by which heat stress-induced mitochondrial adaptabilities are impaired by aging, and identify nutrients/drugs to rescue mitochondrial adaptabilities.

The function and regulation of mechanosensors in skin metabolism

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Skin is a barrier of the body that faces exogenous and endogenous mechanical stimuli. To accommodate mechanical stresses in homeostasis, the skin maintains a high metabolic rate by providing continually the tissues with fresh cells through proliferation and differentiation of epidermal stem cells. In this project, we elucidate the molecular mechanisms that link the mechanical stimuli and epidermal stem cell proliferation especially focusing on the function of mechanosensors. We aim to understand the pathogenesis of chronic skin diseases, such as diabetes-associated skin complaint, which are often developed on a pressure-facing body surface area.

Functional analysis of a transcriptional co-activator that senses mechanical stimulation and promotes tissue fibrosis for developing a new fibrotic treatment method

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When extracellular matrix (ECM) proteins such as collagen are upregulated, various tissues harden and undergo function decrements. This condition is called fibrosis and results from myofibroblasts, which produce ECM proteins such as collagen. I found a transcriptional co-activator that expresses in myofibroblasts, and promotes tissue fibrosis by sensing mechanical stimulation from ECM components. Therefore, in this study, I aim to clarify the mechanism underlying the promotion of tissue fibrosis by the transcriptional co-activator. Simultaneously, I also aim to establish a foundation for a novel method to treat fibrosis by targeting the pathway by which the transcriptional co-activator promotes fibrosis.

Elucidation of the role of mechanosensation for proper circulation of lymph

**NONOMURA Keiko**  
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The lymphatic vasculature is essential for the maintenance of fluid homeostasis, dissemination of immune cells, and lipid reabsorption. Compared to other parts of cardiovascular system, such as the heart and the blood vasculature, physiological importance of mechanosensation in the lymphatic vasculature is poorly understood. It is recently suggested by studies of human patients with familial lymphedema that mechanosensitized channel Piezo1 is required for proper circulation of lymph. In this research, I aim to elucidate physiological role of Piezo1-mediated mechanosensation in the lymphatic system.