Biological Science Laboratories

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Plant Cell Function



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Outline of Research and Education

We conduct extensive research, from basic to applied, concerning protein function, cell morphogenesis, signal transduction and regulation of gene expression in various plants, making effective use of molecular genetics and imaging technology on Arabidopsis thaliana, liverwort, and green algae.

Major Research Topics

1. Dynamic reorganization of microtubule cytoskeleton in response to environmental stimuli leading to stress adaptation

- Pattern formation of bio-polymer networks
- Regulators of microtubule dynamics
- Stress-induced reorganization of microtubule arrays
- Stress-signal transduction leading activation of tubulin kinase
- Novel growth arrest mechanisms by microtubule disassembly

2. Why and how plant pavement cells adopt a jigsaw puzzle-like shape

- Microtubule regulators generating complex cell shapes
- Bio-mechanics for local growth anisotropy
- Physical advantages for complex cell shapes

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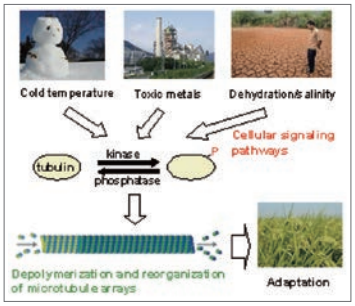

Fig. 1
Environmental stresses remodel the microtubule cytoskeleton by phosphorylation of tubulin subunits.

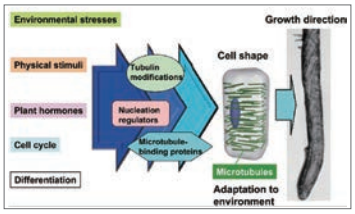

Fig. 2
The plant microtubule cytoskeleton remodels in response to developmental and environmental signals, and controls plant cell shape.

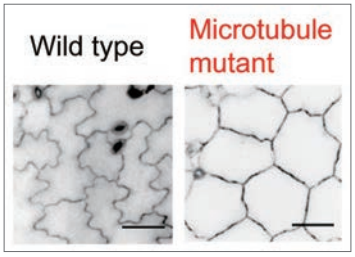

Fig. 3
Microtubules regulate plant cell shapes. Wild-type pavement cells of Arabidopsis cotyledons adopt a jigsaw puzzle-like shape, whereas the mutant cells of the microtubule regulator are polyhedral.

Plant Developmental Signaling


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Outline of Research and Education

Our scientific interests are centered around how plant cells acquire specialized functions and how they coordinately regulate plant growth and life cycles. Each student is engaged in a unique and important project that addresses central questions regarding plant growth and development. Our research is important not only to solve fundamental questions in basic biology, but also to gain the knowledge required to ensure food and energy security.

Major Research Topics

1. How root growth is regulated by endogenous and external cues

Roots have important functions, such as mechanical anchorage, nutrient and water uptake, and interaction with soil environments, and thereby support the life of whole plant bodies. In order to maximize such functions, root tissue organization, growth behavior, and metabolic activities must be precisely controlled by endogenous programs and environmental cues. While past studies have identified key regulatory factors of root development, how they coordinately regulate root growth is largely unknown. To achieve a breakthrough in this, we established a high-magnification live imaging technique to visualize gene expression and cellular/subcellular dynamics at the tip of growing roots for several days. Using this system, we are currently studying genetic and molecular mechanisms integrating endogenous and external cues to regulate root growth in changing environments (Fig. 1).

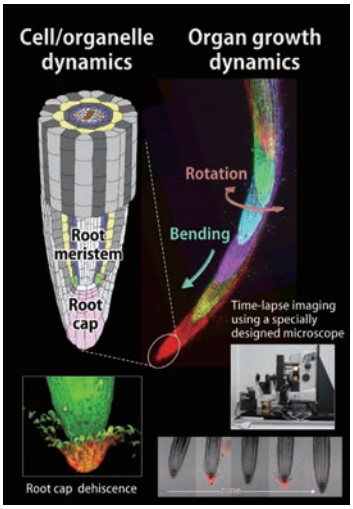

Fig. 1

2. How germ cell morphologies and functions are established in plants

Germ cells, such as eggs and sperm, are functionally specialized for sexual reproduction, and at the same time have specific genomic status enabling pluripotency. Germ cell differentiation in plants takes place deep inside reproductive organs in a relatively short time window, and hence is more difficult to study than somatic cells. We solved this problem through a complementary approach using the flowering plant *Arabidopsis thaliana* and the liverwort *Marchantia polymorpha*. We successfully identified evolutionarily conserved transcription factors that promote female sexual differentiation and egg cell formation in these distantly related land plants. Functional analyses of their target genes will reveal how germ cell-specific morphologies and functions are established in plants (Fig. 2).

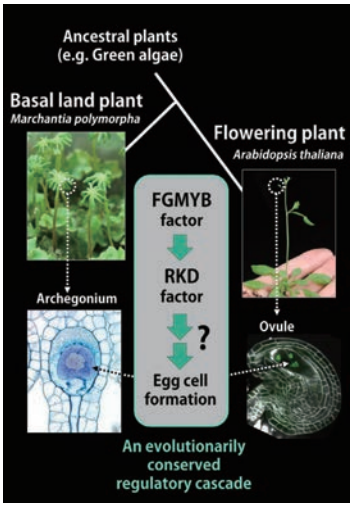

Fig. 2

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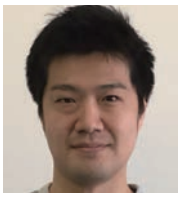
Plant Metabolic Regulation







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Outline of Research and Education

Our laboratory engages in research and education pertaining to the biotechnology needed to resolve the issues facing human beings in the 21st century, such as food, environment, and energy. Especially we are exploring the mechanisms of gene expression regulation for woody cell differentiation using omics technology to develop novel biotechnological tools for the establishment of a sustainable society.

Major Research Topics

1. Molecular mechanisms governing xylem cell differentiation

We identified a key regulator of the xylem vessel differentiation, Arabidopsis VND7 (VASCULAR-RELATED NAC-DOMAIN7), which is a plant-specific NAC domain transcription factor (Fig.1). To understand the molecular mechanism by which xylem vessel formation is regulated, we have been characterizing VND7 and its homologs through various approaches (Fig. 2).

2. Molecular and cell biological approaches to improve woody biomass

We are also conducting genomics, transcriptome, proteome and metabolome studies to reveal the molecular system of plant biomass biosynthesis, using not only model plants but also non-model practical plants.

3. Highly-efficient transgene expression systems in higher plants

Various gene introduction techniques have been developed in higher plants and attempts to produce useful genetically modified plants are actively conducted. However, in practical application, the low expression levels of the introduced genes is a major obstacle. Our laboratories are developing basic technologies to increase the expression levels of genes introduced into plants.

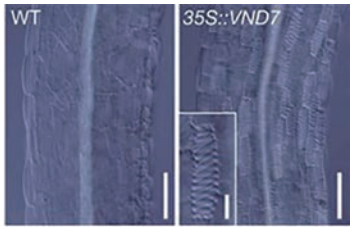

Fig. 1
VND7 acts as a key regulator of xylem vessel differentiation. Overexpression of VND7 induces transdifferentiation of epidermal cells into xylem vessel elements with spiral structures of secondary wall thickening (arrows) in hypocotyl. Bar=100 μm

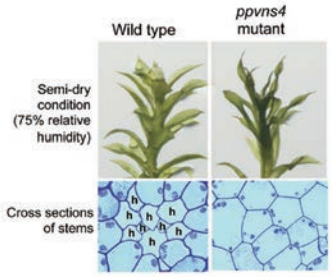

Fig. 2
Moss *Physcomitrella patens ppvns* mutants, a knock out mutant for one of VND-homologous genes, show the malformation of hydroids (h) in stems, thus leading to decreased water transport activity accompanied wilting phenotype under semi-dry conditions.

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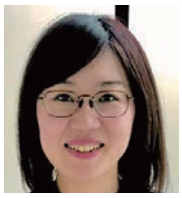
Plant Growth Regulation





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Outline of Research and Education

Plants continuously produce organs throughout their life. This feature renders them distinct from animals, in which organ formation ceases soon after embryogenesis. We aim to understand the mechanisms of DNA polyploidization, stress response and stem cell maintenance that support sustained plant growth under changing environments. Our study will contribute to the development of technologies to increase plant biomass and food production, thereby solving global environmental issues.

Major Research Topics

1. Mechanisms for induction of DNA polyploidization

In many plant species, cells start DNA polyploidization after the cessation of cell division. DNA polyploidization causes enlargement of individual cells and organs; thus, it greatly contributes to plant biomass production. We found that chromatin-level regulation plays a major role in induction of DNA polyploidization in plants. Further studies will help developing technologies to enhance DNA polyploidization in crops and woody plants, aiming to increase food and biomass production (Fig. 1).

2. Plant growth regulation in response to abiotic stress

Plant growth is usually inhibited under stressful conditions because plants need to use energy for coping with stress, rather than for organ growth. We have recently identified the signaling cascade that triggers cell cycle arrest in response to DNA damage and heat stress (Fig. 2). We are studying how this cascade controls cell cycle progression, and generating stress-tolerant plants by modifying the signaling components.

3. Maintenance of plant stem cells

Any plant has a long life span if the developmental program is optimized, and continues to grow throughout its life. This feature is derived from persistent proliferation of pluripotent stem cells scattered throughout the plant body. We are studying the molecular mechanisms of how stem cells are maintained and replenished under changing environments to understand plant vitality (Fig. 3).

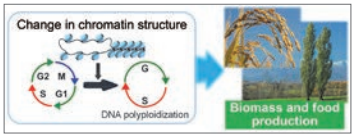

Fig. 1
Increasing plant biomass by enhancing DNA polyploidization.
Changes in chromatin structure and cell cycle progression induces DNA polyploidization.

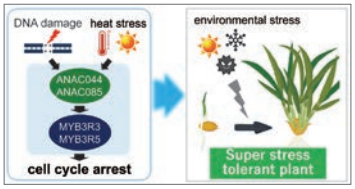

Fig. 2
A signaling module inducing cell cycle arrest in response to abiotic stresses.
Transcription factors MYB3R3/5 cause G2 arrest in response to DNA damage and heat stress. Suppression of this module will enable us to generate super stress-tolerant plants.

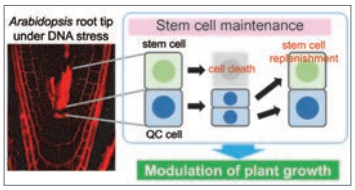

Fig. 3
Stem cell maintenance in the root tip.
Stem cell death, which occurs in response to DNA damage, is accompanied with the division of a neighboring QC cell, thereby replenishing stem cells.

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Plant Stem Cell Regulation and Floral Patterning


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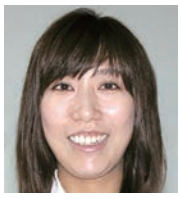
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Outline of Research and Education

We are interested in a holistic view of gene regulation in plant reproduction, which leads to developmental robustness and coordination. We explore signaling and epigenetic control in stem cell maintenance, environmental response and fertilization. To reveal molecular mechanisms, we use *Arabidopsis* as a model plant for genetic, reverse-genetic, biochemical and genomics approaches, as well as Brassicas and rice, to study conservation and diversification. Our students work at the frontiers of plant molecular genetics, developing their research, presentation and writing skills.

Major Research Topics

1. Proliferation, differentiation and senescence of floral stem cells

Flowers originate from self-renewing pluripotent stem cells in the floral meristems (Fig. 1). In flower development, the stem cell activity is terminated in multistep pathways mediated by multiple transcription factors. The proliferation, differentiation and senescence of stem cells are regulated by a well-coordinated interplay of phytohormone signaling and epigenetic regulation, leading to spatiotemporal-specific gene regulation. We study downstream cascades of the key transcription factors controlling stem cell termination, flower organogenesis and senescence (Fig. 2).

2. Environmental response, memory and forgetting in plants

We study how plants memorize environmental temperature and light conditions and reveal the molecular mechanisms that confer the plasticity and robustness of the cascades under various environmental stimuli. These studies will serve as a basis of plant growth optimization for improved crop plant yields (Fig. 3).

3. Epigenetic regulation in sexual reproduction

Heterosis, or hybrid vigor, is the increased function of any biological quality in a hybrid offspring. We study the epigenetic mechanisms of heterosis using Arabidopsis accessions. We also study epigenetic-mediated genomic imprinting and self-imcompatibility.

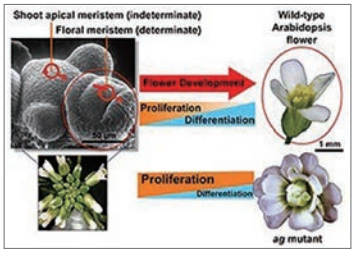

Fig. 1
Arabidopsis flower development
In flower development, the stem cell activities in the floral meristem are terminated (determinate), while the shoot apical meristem continues to grow.

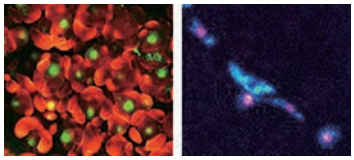

Fig. 2
Imaging of key transcription factors in floral meristems (left) and a differentiated myrosin cell (right)

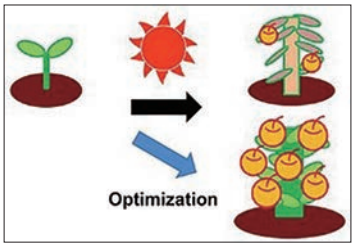

Fig. 3
Plant growth optimization
By revealing the mechanisms of floral stem cell regulation and environmental responses, we will develop a molecular basis for plant growth optimization for higher crop yield.

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Plant Physiology


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Outline of Research and Education

Circadian clocks are molecular mechanisms used by plants and other organisms to predict and respond to environmental changes. Approximate 24 hour circadian rhythms affect many aspects of plant physiology, including cell elongation and photoperiodic flowering. To pinpoint how clocks function individual cells and tissues levels, we develop new methods for analysing gene expression with high spatiotemporal resolution. This is accompanied by the application of these to the control of photoperiodic flowering. Through this research, we seek a better understanding of plant physiology and development. We also attempt to identify gaps in our current understanding which can be addressed with greater precision.

Major Research Topics

1. Dissection of circadian clock functions at organ, tissue and cellular levels

Circadian clocks are used to predict the timing of transitions between day and night, and different seasons. In plants, the circadian clock modulates cell elongation, leaf movement, and flowering. We have shown that these responses can be explained by tissue-specific functions of circadian clocks. To explore the tissue and cell-type-specific functions of circadian clocks in further detail, we are investigating circadian rhythms with high spatiotemporal resolution and reveal signalling mechanisms with clear biological significance

2. Understanding and controlling photoperiodic flowering via the circadian clock

Photoperiodic control of flowering is a regulatory mechanism of key physiological importance mediated by the circadian clock. The molecular mechanisms by which the flowering hormone, florigen, regulates flowering have been extensively studied, but there are still questions to be answered regarding the integration of environmental signals into the circadian clock, and how seasonal information is extracted from circadian rhythms. We are assessing how light, temperature, nutrients and other external factors regulate photoperiodic flowering through circadian rhythms; while also applying this knowledge to control crop flowering time without genetic modification.

3. New technologies for high spatiotemporal analysis

To achieve high spatiotemporal analysis, we are developing new methods to precisely examine the function of the circadian clock. These include specific tissue/cell isolation, non-invasive measurement of tissue-specific gene expression, and an algorithm for a time-series single cell transcriptome. These new approaches provide novel ways to test our current understanding

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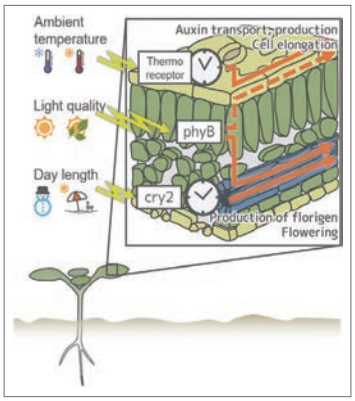

Fig. 1
Tissue-specific environmental responses through cell-type specific clocks. We found circadian clock functionality in specific tissues is required for specific physiological responses

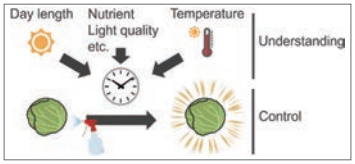

Fig. 2
Understanding clock-mediated flowering mechanisms allows for the manipulation of crop flowering times.

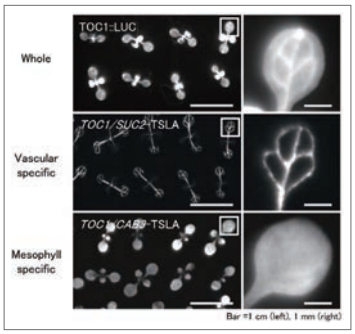

Fig. 3
Tissue-specific luciferase assay. Many clock genes including *TOC1* are expressed ubiquitously (top). Our technique enables us to measure tissue-specific dynamics of *TOC1* (middle and bottom), and this analysis shows tissue-specific circadian rhythms.

Plant Immunity

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Outline of Research and Education

In nature, plants host a rich diversity of microbes, ranging from mutualistic symbionts to pathogens. The mode and outcome of plant-microbe interactions, including crop disease epidemics, are profoundly influenced by environmental factors, such as light, temperatures, water and nutrients. We aim to decipher the mechanisms by which plants sense and integrate microbial and abiotic cues to monitor and manage their associations with microbes, and also how microbes infect and influence host plants, under fluctuating environments. Our major research topics involve immune receptor signaling, biotic-abiotic stress signaling crosstalk, and functional significance and infection strategies of pathogenic and endophytic microbes. We hope our studies will reveal key principles underlying host-microbe interactions and contribute to developing human and biological resources for future sciences and sustainable agriculture.

Major Research Topics

1. Danger sensing and signaling in plant immunity

2. Signal integration between biotic and abiotic stress responses

3. Beneficial and pathogenic microbes in plants

4. Plant-associated microbiomes

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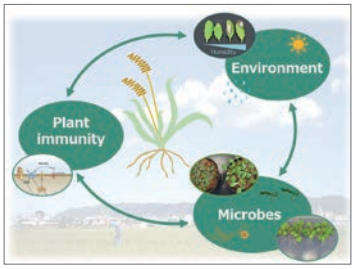

Fig. 1
Host-microbe-environment interactions provide a critical basis for host survival and health, and represent key questions in life sciences. We aim to better understand the underlying molecular principles and mechanisms in plants.

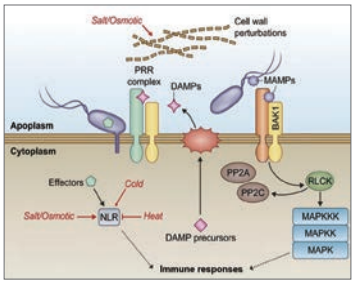

Fig. 2
A basic framework for plant immunity signaling and its environmental modulation. Cell surface detection of microbe/damage-associated molecular patterns (MAMPs/DAMPs) by pattern recognition receptors (PRRs) triggers intracellular defense signaling. We pursue the mechanisms by which plants integrate biotic and abiotic stress signaling. See Saijo and Loo, *New Phytologist* 2020.

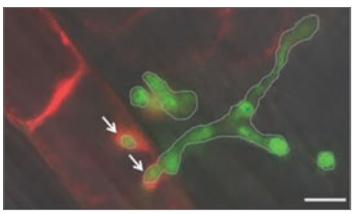

Fig. 3
Root colonization of endophyte *Colletotrichum tofieldiae* (Ct). Confocal microscopy reveals invasion of GFP-expressing Ct (green, labeled by dotted lines) into *Arabidopsis* roots (VAMP722-mRFP, Red). Intracellular fungal hyphae inside root cortical cells are enveloped by host membranes (PIP2A-mCherry, arrows). Bar = 10 μm.

Plant Symbiosis

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Outline of Research and Education

Parasitic plants - major agricultural constrains in the world

Parasitic plants are able to parasitize other plants and rely on their hosts for water and nutrients. Several parasitic plants in the Orobanchaceae family, such as *Striga* (Fig. 1) and *Orobanche* spp., cause enormous damage to world agriculture because they parasitize important crops and vegetables. We are investigating molecular mechanisms underlying plant parasitism using the model parasitic plants *Phtheirospermum japonicum* and weedy parasite *Striga* spp. By combining molecular, genetic, cell biology and genomic approaches, we aim to understand the nature of parasitism and eventually develop novel control methods for weedy parasites.

Fig. 1
Sorghum field infested by *Striga* spp. (pink flowers) in Sudan

Major Research Topics

1. Identification of genes involved in haustorium formation

Parasitic plants form specialized invasive organs called "haustorium". The haustorium invades host roots, and eventually forms a vasculature connection between the host and the parasite to assimilate host nutrients (Fig. 2). To identify the genes involved in haustorium formation, forward and reverse genetic tools in *P. japonicum* were established. Screening of *P. japonicum* mutants which lack haustorium formation and identification of the causal genes by next-generation sequencing (Fig. 3) will isolate the essential genes in the haustorium formation. Furthermore, the genes upregulated during haustorium formation will be reverse-genetically analyzed.

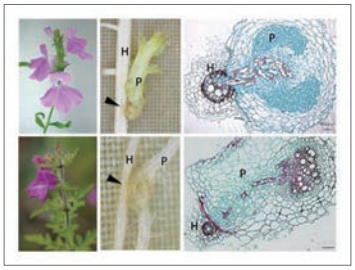

Fig. 2
Obligate parasite *Striga her-monthica* (upper panels) and faculta-tive parasite *Phtheirospermum japon-icum* (lower panels). Photos of flowers (left), host invading parasitic plant root (middle) and cross section of haustorium (right). H: host, P: parasite. Arrowheads indicate haustoria.

2. Plant-plant communication via small-molecular weight compounds

Parasitic plants recognize their hosts via small-molecular weight compounds secreted from the host plant (Fig. 4). For example, the obligate parasite *Striga* germinates in response to the plant hormone strigolactones. The haustorium formation is induced by derivatives of cell wall lignin; however, the nature of haustorium inducers has not been clearly understood. We are trying to identify novel haustorium inducing compounds.

3. Comparative genomics of parasitic plants

Recent progress in next-generation sequencing technology enables us to acquire the complete genome sequence of any plant. We sequenced the whole genomes of *Striga* and *P. japonicum*. By examining these genome sequences, we found that parasitic plants have experienced evolutional events such as expansion of specific gene family and horizontal gene transfers from hosts. How did the plants obtain new genes, increase the copy numbers and eventually acquire a new trait? What is the genetic diversity among *Striga* species in Africa? We analyze genome evolution using bioinformatics tools.

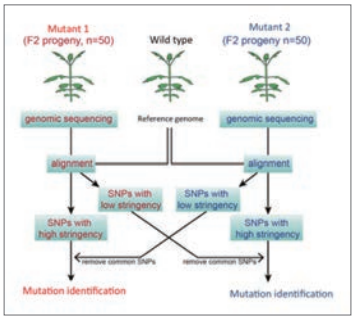

Fig. 3
Identification of the mutant causal genes using a next-generation sequencer

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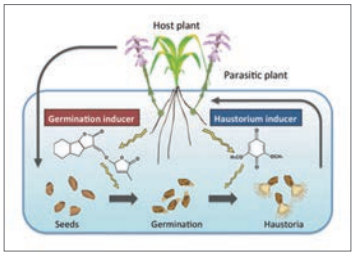

Fig. 4
Chemical communication between host and parasitic plants

Plant Secondary Metabolism

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Outline of Research and Education

Plant secondary metabolism (also called "specialized metabolism") produces compounds having several bioactivities such as resistance factors against various environmental stresses in plants, as well as health benefits for humans. Secondary metabolites are widely diversified in their chemical structures in nature (Fig. 1), since plants have adapted to environmental niches during long evolutionary periods using varied strategies such as gene duplication and convergent evolution of some key genes, which contributes to chemical diversity. Our laboratory focuses on model plants, crop species and medicinal plants for i) the analysis of the natural diversity of secondary metabolites, and ii) the functional genomics approach by translational analysis of omics studies (genomics, transcriptomics and mass spectrometry-based metabolomics). The specific goal is identifying key factors of natural chemical diversity and regulatory roles in plant secondary metabolism to enable the metabolic engineering of beneficial compounds.

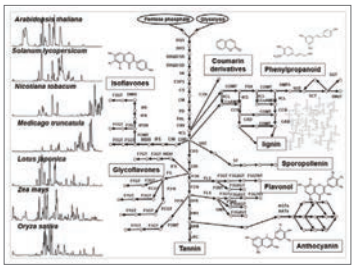

Fig. 1
Metabolic network of plant polyphenolic biosynthesis and their chemical diversity between plant species

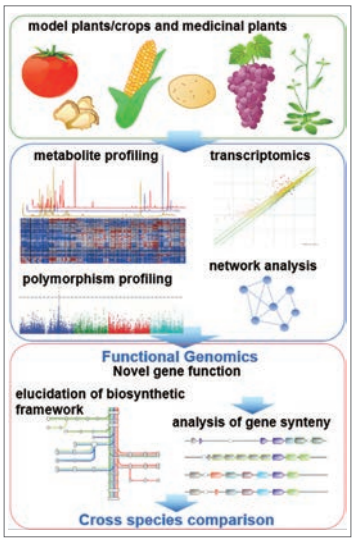

Fig. 2
Omics-based translational analysis using model plants and crops

Major Research Topics

1. Functional genomics approach by omics-based translational analysis

After completion of full-genome sequencing of huge array of plant species, the complete biosynthetic framework of each plant species still needs to be elucidated, since genome information is not sufficient to compute the size and framework of plant metabolism. We therefore perform metabolomic analysis to screen qualitative differences of metabolite levels between different species, tissues and natural mutants for refinement of recent models of biosynthetic framework (Fig. 2). After illustration of metabolic framework, genome and transcriptome data, as well as genome-wide resources such as quantitative trait locus (QTL) lines and wild accessions for genome-wide association studies (GWAS), are employed for translational analysis. We focus on the discovery of key genes involved in the creation of chemical diversity, and production of beneficial compounds.

2. Cross species comparison of the neo-functionalized genomic region

The range of genetics-based strategies for characterization of key genes described above provide several genes and genomic regions involved in neo-functionalization of plant secondary metabolism. "Neo-functionalization", which produces a totally new function after a gene duplication, is a key factor of functional gene divergence. We therefore focus on the species-specific duplicated genes in these key genome synteny regions in order to discover new functional genes in plant secondary metabolism.

3. Regulation of metabolic networks during nutritional stresses

Nutrient deficiency in soil causes severe reduction in growth with low yields and crop quality. We investigate metabolic and gene expression changes of plants grown under nutrient deprivation stress. This study aims to: i) make an index of time-dependent metabolic changes, ii) evaluate the robustness of metabolic networks, and iii) find species-conserved metabolic makers for the effective breeding of plants having high nutrient-use efficiency or tolerance to nutritional stress.

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Molecular Signal Transduction

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Outline of Research and Education

Signal transduction is indispensable for organ development and homeostasis. Hormones and neurotransmitters induce a variety of cell responses mediated through membrane receptors and intracellular signaling pathways. Impairment of the signal transduction often causes disease. And with this, many drugs targeting these signal components are widely used today. Our laboratory is interested in cellular signaling systems with special emphasis on heterotrimeric G proteins. In our laboratory, faculty and graduate students are dedicated to cutting-edge scientific research and work towards a better understanding of how the human body functions and the alleviation of human disease.

Major Research Topics

1. Cellular functions and regulatory mechanisms of G protein signaling

2. Monoclonal antibodies against orphan adhesion GPCRs involved in tumorigenesis and neural function

3. Role of adhesion GPCRs in breast cancer

4. Formation and function of primary cilia

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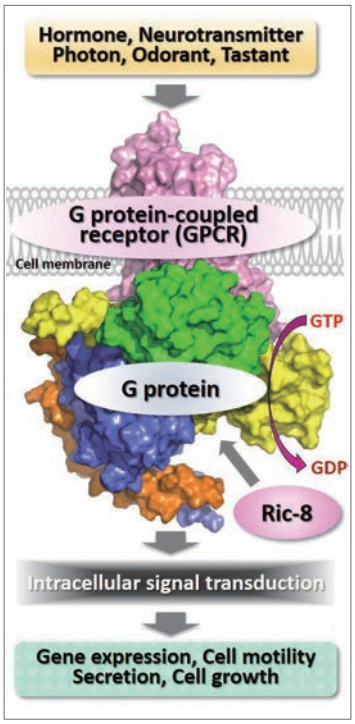

Fig. 1
Signal transduction mediated by G protein-coupled receptor

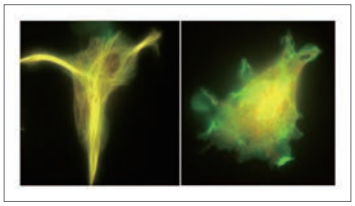

Fig. 2
G protein/PKA signal-regulated dynamics of a cytoskeleton in neuronal progenitor cells

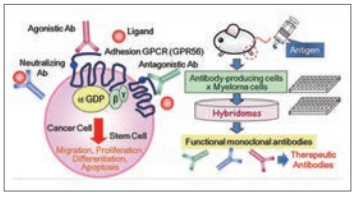

Fig. 3
Monoclonal antibody against orphan GPCR as a tool for signal analysis

Functional Genomics and Medicine

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Outline of Research and Education

In 1991 at Kyoto University, Ishida et al. discovered a novel gene in a project for the elucidation of the molecular mechanisms involved in the self-nonself discrimination by the immune system, and named it programmed death-1 (PD-1), hoping that it somehow plays a pivotal role when self-reactive (harmful) T lymphocytes (T cells) commit suicide by undergoing apoptosis. PD-1 is a type I transmembrane protein expressed on T cells that are activated by antigenic stimulation. Initially, the physiological function of PD-1 was elusive, but it was shown later that PD-1 downregulates excessive immune reactions. Recently, T. Honjo et al. (Kyoto Univ.) discovered that the cytotoxicity of T cells against some cancer cells can be induced by the antibody-mediated blockade of the above physiological function of PD-1. This anti-cancer strategy is now being widely performed in clinics of many countries, and the Nobel Prize 2018 in physiology and medicine was awarded to T. Honjo (and J.P. Allison). Unfortunately, however, the roles of PD-1 in self-nonself discrimination by the immune system still remain elusive. We conduct our research in the fields of immunology and molecular genetics to identify these roles.

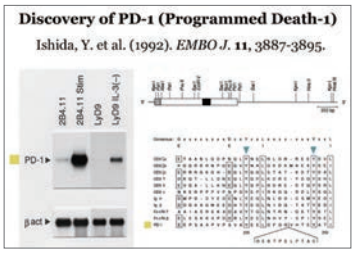

Fig. 1
Some people say that PD-1 was discovered only by chance.

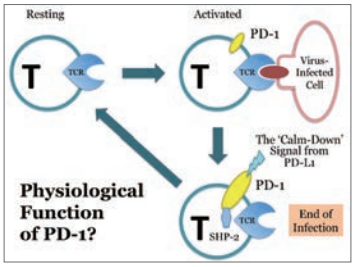

Fig. 2
PD-1 negatively regulates excessive immune reactions.

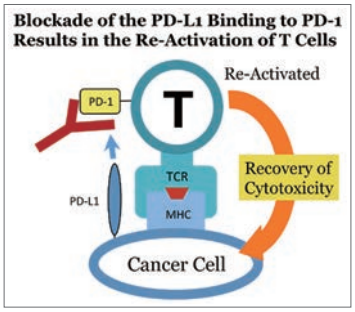

Fig. 3
Cancer immunotherapy using the anti-PD-1 blocking antibody.

Major Research Topics

1. Elucidation of the real physiological functions of PD-1

It is very strange that we can cure cancer by blocking the physiological functions of PD-1. What is then PD-1 doing in our body? Is PD-1 on our side (protecting us) or on the side of cancer cells (protecting them)? People believe that PD-1 is a negative regulator of the immune responses, but what kind of signals in the immune system is PD-1 suppressing? (Obviously, PD-1 is not an omnipotent negative regulator in the immune system) To answer these questions, we perform experiments in immunology and molecular biology by using a variety of genetically modified animals (including PD-1 knockouts).

2. Development of novel strategies in cancer immunotherapy

Cancer immunotherapy based on the blockade of the physiological functions of PD-1 is effective only upon a limited number of cancer patients. For instance, only about 20% of lung-cancer patients and only about 30% of melanoma patients show good responses to such a PD-1-blocking strategy. We try to improve this low efficacy of current cancer immunotherapy by creating a variety of "oncolytic" recombinant retroviruses.

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Tumor Cell Biology

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Outline of Research and Education

We focus on the molecular mechanisms controlling proliferation, differentiation, and death of mammalian cells, and study the connection between cell cycle progression and oncogenesis, as well as differentiation, proliferation, and leukemogenesis in hematopoietic cells. These findings can be applied to regenerative medicine and cancer research. We use the following experimental systems:

- in vitro culture systems using mouse and human cell lines
- in vitro differentiation systems using ES cells and primary cultures
- mouse model systems using knockout and transgenic mice

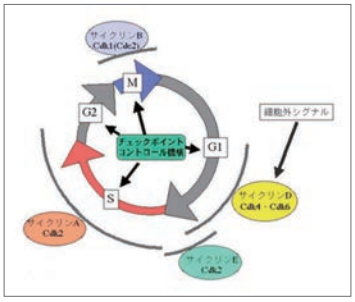

Fig. 1
Cell cycle and cyclin/Cdk complexes

Major Research Topics

1. Cell cycle control and oncogenesis

- Cell cycle control and oncogenesis: During the cell cycle, whether cells should proliferate or stop growing and prepare for differentiation is decided at the G1 phase. Therefore, we investigate the function of molecules that promote or inhibit the progression of the G1 phase such as cyclins, Cdks, Cdk inhibitors, and Rb tumor suppressor gene products (Fig. 1).
- Checkpoint control: The checkpoint mechanism is a means of monitoring and controlling the progression of the cell cycle. The central role in this checkpoint mechanism is played by the tumor suppressor gene product, p53. Recently, members of the p53 gene family, p63 and p73, have been identified. We are interested in the role of these molecules not only in oncogenesis, but also in the developmental program including morphogenesis (Fig. 1).
- Cancer and the cell cycle: Since cancer cells grow abnormally, they generally have abnormalities in the cell cycle control. We analyze the key molecules involved in cell proliferation, G1 regulation, and checkpoint control, and investigate the mechanisms involved in the abnormal growth of cells and cellular oncogenesis.

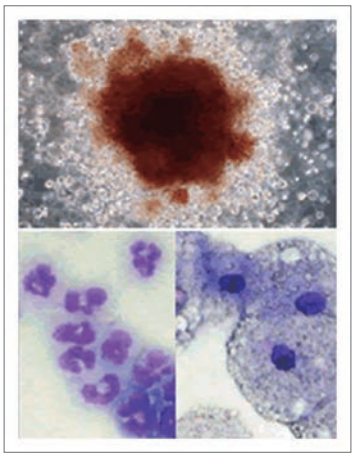

Fig. 2
A group of erythrocytes and leukocytes (upper), neutrophils (lower left) and macrophages (lower right), which were induced to differentiate from ES cells in vitro

2. Leukemogenesis

We investigate the molecular mechanisms underlying leukemogenesis, focusing on AML (acute myeloid leukaemia), MDS (myelodysplastic syndromes), and CML (chronic myeloid leukaemia).

3. Hematopoietic stem cells

We perform studies on hematopoietic stem cells present in the bone marrow, with the aim of developing in vitro amplification methods for hematopoietic stem cells. The results of these studies can be of benefit to regenerative medicine as well as leukemia research.

Fig. 3
A chimeric mouse generated by infusion of genetically modified ES cells

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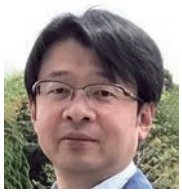
Molecular Immunobiology



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Outline of Research and Education

Our body has an immune system to fight against microbial pathogens such as viruses, bacteria, and parasites. There are two arms of the immune system; innate and adaptive immunity. The innate immune system is the first line of host defense that detects invading microbial pathogens and plays a critical role in triggering inflammatory responses as well as shaping adaptive immune responses. In spite of its role in host defense, aberrant activation of innate immune responses is closely associated with exacerbation of inflammatory diseases, autoimmune diseases and cancer. Our aim is to uncover molecular mechanisms that control innate immune responses using tools of molecular and cell biology, bioinformatics and genetically modified mice, and seek a way to control immune diseases.

Major Research Topics

1. Analysis of innate immune signaling pathways

The innate immune system employs germline-encoded pattern-recognition receptors (PRRs) for the initial detection of microbes. PRRs distinguish self from non-self by recognizing microbe-specific molecular signatures known as pathogen-associated molecular patterns (PAMPs), and activate downstream signaling pathways that lead to the induction of innate immune responses by producing inflammatory cytokines, type I interferon (IFN) and other mediators. Mammals have several distinct classes of PRRs including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs), C-type lectin receptors (CLRs) and intracellular DNA sensors. Among these, TLRs were the first to be identified, and are the best characterized. The TLR family comprises 13 members, which recognize distinct or overlapping PAMPs such as lipid, lipoprotein, protein and nucleic acid (Fig. 1). We are focusing on the recognition mechanism of microbial components by PRRs and their signaling pathways, and understanding their roles in immune responses.

2. Analysis of RLRs

RLRs such as RIG-I and MDA5 are cytoplasmic RNA helicases that detect infection of RNA viruses. Upon detection of RNA virus, RLRs trigger intracellular signaling pathways by recruiting a mitochondria-localized adapter IPS-1, which further activates the transcription factors NF-kB and IRF3 that control expression of antiviral genes, including IFN and inflammatory cytokines (Fig. 2). We seek to understand molecular mechanisms underlying RLRs-mediated antiviral innate immune responses.

3. Analysis of sensing mechanisms of endogenous molecules by PRRs (Fig. 3)

Recent evidence has shown that innate immunity can react with endogenous molecules derived from necrotic cell death and this reaction is associated with inflammatory diseases. In addition, innate immunity also senses environmental factors such as asbestos and pollen, and causes cancer and allergic responses, respectively. We are seeking the recognition mechanisms of these molecules by innate immunity and its role in diseases.

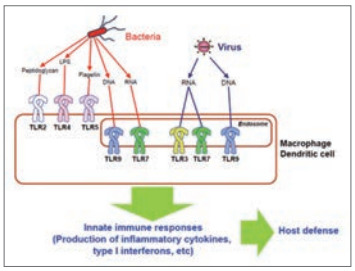

Fig. 1
Recognition of microbial components by Toll-like receptors (TLRs)

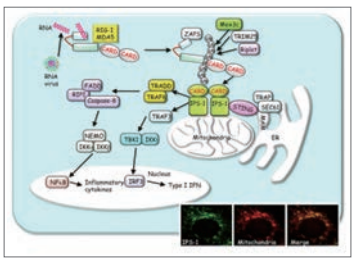

Fig. 2
Signaling pathways through RLRs, cytosolic sensors for RNA viruses

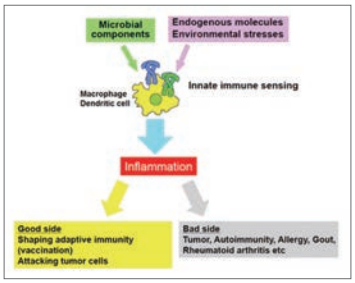

Fig. 3
Recognition of non-infection agents by innate immunity and its relevant in diseases

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Molecular Medicine and Cell Biology


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Outline of Research and Education

The cellular membrane is the essential component of cells that distinguishes the inside and the outside of cells. While the membrane receives all of the stimulus affecting the cells, how it behaves is not well understood. Our lab focuses on the membrane-binding proteins connecting the membrane to the intracellular signaling for varieties of cellular functions including proliferation and morphological changes, using biochemical, cell biological, biophysical, and information techniques. The roles of lipid composition of the membrane, including the saturation or unsaturation of fatty acids, are examined using the membrane-binding proteins.

Major Research Topics

1. Elucidating cell-shape dependent intracellular signaling

The intracellular signaling cascade became understood by observing molecule-molecule interactions. However, the spatial organization of these signaling cascades had not been well studied. We found the BAR domain superfamily proteins that remodel membrane shape and then, presumably, dictate the intracellular signaling cascades. Thus, the important questions are how the BAR domain superfamily proteins are regulated, and how they assemble the downstream molecules.

2. Searching for new membrane binding proteins

Given the importance of membrane lipids as essential components of cells, we suppose there are many lipid-binding molecules that have not been clarified. We are searching for novel lipid-binding proteins using a variety of methods.

3. The importance of fatty acids in the membrane

Another point for understanding the cellular membrane is the importance of fatty-acid tails of lipids. Although the importance of saturated or unsaturated lipids in nutrients is well-known, the mechanism behind this importance is not understood at molecular levels in cell biology. We examine how fatty acids are important in intracellular signaling including that for cancer, using the proteins listed above.

4. Information science for cell biology

Image analysis using deep learning enables the recognition of the features stipulated by researchers. Such image analysis will reveal previously unrecognized features of protein localization for cellular morphology and will relate the cell morphology to cellular functions.

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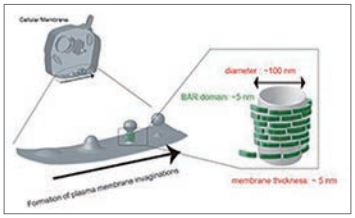


Fig. 1
Location of BAR domain functions in cells. The BAR domains function as polymers at submicron-scale invaginations, such as clathrin-coated pits and caveolae, as well as in protru-sions, including filopodia and lamel-lipodia. The typical scales for clathrin-coated pits and caveolae are 100-200 nm and 50-100 nm in diameter, respectively. The BAR domains have typically been approximated as arcs of 20-25 nm in length with a diameter of 3-6 nm. The membrane thickness is typically approximately 5 nm.

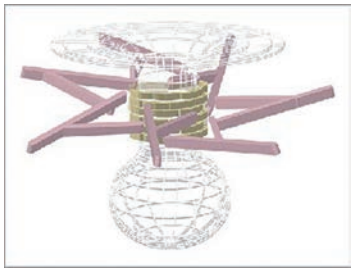


Fig. 2
Wire-frame model of the clathrin-coated pit. The BAR proteins are shown in yellow, and the actin cytoskeleton is shown in magenta. The membrane is in wire-frame. The actin filaments are thought to be finely organized on the nano-scale membrane invaginations of the clathrin-coated pits.

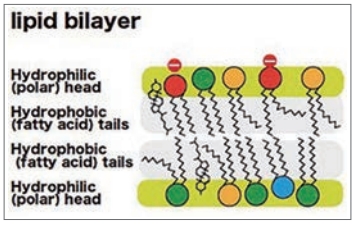
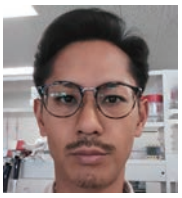


Fig. 3
Schematic diagram of the cellular membrane. Each lipid molecule con-sists of one hydrophilic head and two hydrophobic fatty-acid tails. There are varieties of combinations of the head, such as serine, ethanolamine, etc., and various saturated and unsaturated fatty acids, such as palmitic acid (saturated), oleic acid (monounsaturated), etc.

RNA Molecular Medicine



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Outline of Research and Education

Advances in genomics technologies have transformed research and development strategies in biology and biomedicine, allowing us to access genetic information encoded in our DNA (Fig. 1). Our laboratory is interested in understanding how individual genes form large regulatory networks to control biological processes. In particular, we study how regulatory non-coding RNAs including microRNAs (miRNAs) contribute to gene regulation and how their misregulation leads to human health problems.

Research in our laboratory relies on a combination of traditional and modern techniques including biochemistry, genetics and computational biology. Students are expected to learn how to carefully interpret analysis results and develop strategies to answer biological questions by utilizing existing technologies or devising new techniques.

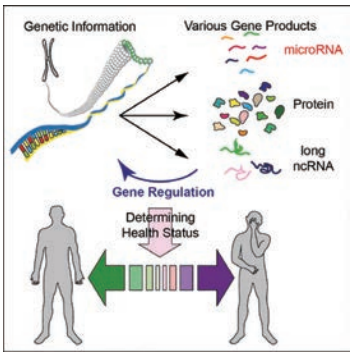

Fig. 1
Gene regulatory networks and their importance in normal development and physiology

Major Research Topics

1. How is expression of miRNAs controlled?

We have witnessed a paradigm shift in the research of gene regulation, and the importance of post-transcriptional regulation of protein-coding genes has now been broadly recognized. Expression of miRNAs should also be regulated at multiple levels (Fig. 2). Precise regulation of miRNA levels is important because misregulation of miRNAs often results in human disease. We study how miRNA levels are controlled under healthy and diseased conditions using genomic and biochemical techniques, and examine their biological significance at the cellular and organismal levels (Fig. 3).

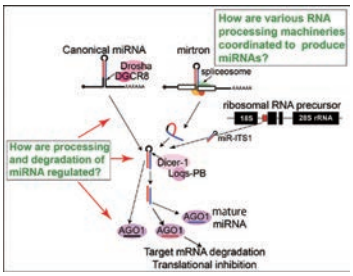

Fig. 2
microRNA processing pathway

2. Why are there many ways to produce miRNAs?

We discovered novel mechanisms of miRNA processing that use machineries known to produce other RNA families, such as mRNA introns and ribosomal RNAs (Fig. 2). This means that RNA processing machineries often have unexpected roles in gene regulation. We study the biological significance of non-canonical roles of various RNA processing pathways.

3. How have small RNA pathways changed in evolution?

Our previous studies revealed a variety of small RNA pathways including those that are only present in particular organisms functioning as natural defense systems (Fig. 2). To capture the full diversity of animal small RNA pathways, we are sequencing small RNAs from various animals by next generation sequencing. Discoveries of new small RNA pathways may pave the way for the development of novel technologies that complement the current CRISPR or RNA interference technologies.

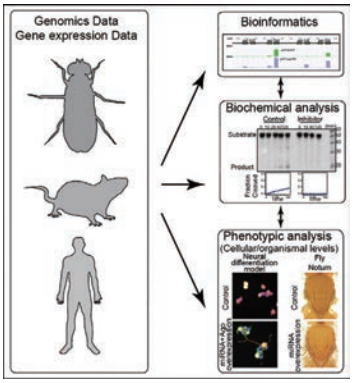

Fig. 3
Outline of research strategies

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Stem Cell Technologies

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Outline of Research and Education

Pluripotent stem cells, such as embryonic stem (ES) cells and induced pluripotent stem (iPS) cells, have the abilities of unlimited self-renewal and multiple differentiations into all the tissue cells of the body. Therefore, these stem cells find potential application in regenerative medicine and drug discovery, and it is very important to strictly regulate this potent differentiation ability to induce multi-step differentiation of these stem cells toward functional tissue cells. During mammalian development, cells differentiate to form precise 3D structures of organs. Understanding of this process may contribute to the development of in vitro differentiation methods. Our goal is to understand the mechanisms of stomach and lung development to perform in vitro differentiation of pluripotent stem cells into these tissue cells. Moreover, we plan to develop in vitro disease models of these organs and technologies for regenerative medicine in the near future.

Major Research Topics

1. Generation of gastric tissues and their disease models

Although the stomach is a major organ in our body, the mechanisms of its development are not well known. During early development, a primitive gastric tube developed from early endoderm is converted to stomach primordium, and further matures to fundus and antrum tissues covered with gastric glands. Recently, we developed an in vitro differentiation method of mouse ES cells to whole stomach tissue (Fig. 1). We think that this method could be a powerful tool to study the mechanisms of stomach development as well as serve as a unique model for various diseases such as gastric cancer (Fig. 2). We are currently investigating the mechanisms of gastrointestinal development, and studying these mechanisms using our in vitro model.

2. Differentiation of lung tissue and tissue regeneration

The lungs emerge as lung buds from the early gastric tube during development. These primordia proliferate, morphologically divide into multiple branches with the mesenchymal layer, and further differentiate into several kinds of epithelial cells to fulfill respiratory functions (Fig. 3). Recently, differentiation methods for these lung tissues have been investigated in the scientific community. We are also studying novel differentiation methods for these respiratory tissues.

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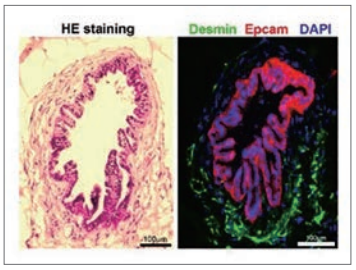

Fig. 1
Stomach tissue differentiated from mouse ES cells *in vitro* by 3D culture method. (Left) HE staining of the differentiated stomach organoid (day 56). (Right) Immunofluorescent staining of stomach organoid with Epcam antibody (red), Desmin anti-body (green), and DAPI (blue) for epidermis, mesenchyme, and nuclei, respectively. Stomach organoid with gastric glands and mesenchyme can be differentiated from ES cells *in vitro*.

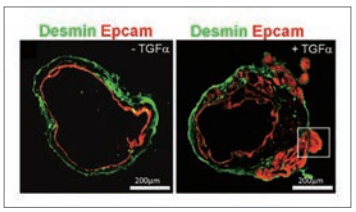

Fig. 2
A stomach disease model using *in vitro* differentiation method. (Left) Healthy control model. (Right) Ménétrier's disease model with massive gastric folds. This disease model can be generated by addition of TGF-α after day 28 of *in vitro* differentiation.

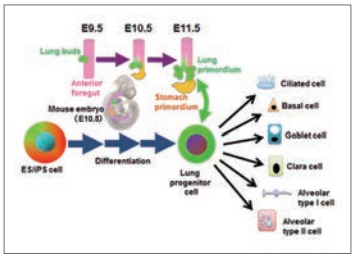

Fig. 3
During lung development, lung progenitor cells are generated in lung buds and can differentiate into various functional epithelial cells of the lung. These lung progenitor cells can be differentiated from pluripotent stem cells *in vitro*.

Developmental Biomedical Science

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Outline of Research and Education

The central nervous system, a critical organ for controlling individuals' body conditions, is comprised of a variety types of neurons, and its generation undergoes a number of regulatory steps mainly at the embryonic stages. We intend to elucidate the molecular mechanisms leading to this complexity by employing chick and mouse embryos, and mouse embryonic stem (ES) cells as experimental systems.

We are also interested in the homeostasis of functional neurons. By using model mice which develop particular inherited retinal diseases, we envisage proposing novel therapeutics for these related dystrophies.

Overall, our research program aims to be influential in cell and developmental biology and will furthermore be both scientifically and technically cross-disciplinary spanning basic biology and biomedical sciences.

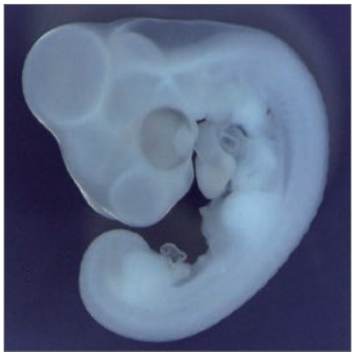

Fig. 1
A chick embryo incubated for 4 days

Major Research Topics

1. Mechanisms leading to pattern formation and size control of the developing central nervous system

The neural tube is the embryonic tissue of the central nervous system where a number of functional neurons are produced and distributed in a quantitatively and positionally precise manner. This accuracy is mainly achieved by extracellular molecules including BMP, Wnt and Sonic Hedgehog (Shh). These molecules form gradients within the tissue and induce different types of neurons. In addition to the fate assignments, these signal molecules control proliferation of the cells. We are particularly interested in the relationship between cell fate determination and the proliferation of the cells.

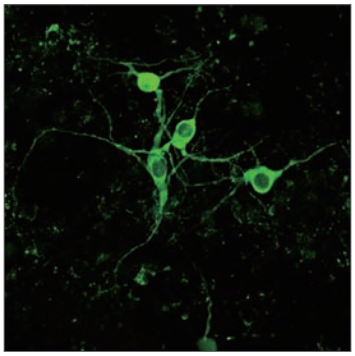

Fig. 2
Dopaminergic neurons cultured in vitro

2. Homeostasis of postnatal cells

How functional cells are maintained is also an important question. We possess genetically mutated mice that model retinal degeneration. While these mutant mice develop to normal retinal structure, the retina start to degenerate once their eyes open soon after birth. We are seeking the primary mechanisms leading to this retinal degeneration by using high-throughput sequence analysis and try to develop novel therapeutic methods.

In addition, our recent study has suggested that the retinal degeneration coincides with many more dystrophies in other organs. We are therefore aiming to propose further therapeutic methods through systemic analysis of these model mice.

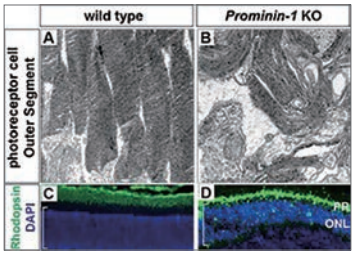

Fig. 3
Eye phenotype in Prominin-1 (Prom1) deficient mice. The outer segments are degenerated (A, B), and Rhodopsin proteins are misplaced in the photoreceptor cells of the Prom1-knockout eyes (C, D)

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Organ Developmental Engineering

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Outline of Research and Education

In mammals, until the eight-cell embryo stage, fertilized eggs have totipotency, meaning that each cell can differentiate into all kinds of cell. In blastocyst-stage embryos just before implantation, the cells' fates are divided into the trophectoderm (TE), which will develop into placental tissue, and the inner cell mass (ICM), which has pluripotency in that its cells will develop into three germ layers, including germline cells. Embryonic stem cells (ESCs) were established from ICM, promoting the study of regenerative medicine and led to the discovery of induced pluripotent stem cells (iPSCs). We combine these early embryos, ESCs/iPSCs, and developmental technology with the aim of performing basic studies that will lead to regenerative medicine using animal models.

Major Research Topics

1. Model of organ formation using xenogeneic chimeras

Xenogeneic chimeras containing both mouse and rat cells were generated using blastocysts and ESCs (Figs. 1, 2). When we injected rat ES cells into blastocysts of nu/nu mice lacking a thymus, we could produce a rat thymus in chimeric animals. This indicates the formation of an organ from ES cells in xenogeneic conditions. Although this rat thymus could educate T-cells (Fig. 3), it was smaller than that of a mouse, and the functions of the educated T-cells were unclear. On the other hand, we could detect rat spermatozoa in mouse←rat ES chimeric testes. Rat pups were generated from rat spermatozoa in the xenogeneic chimeric testes by intracytoplasmic injections, and the normal germline potential of rat spermatozoa in the xenogeneic chimeric testes was demonstrated. Findings of the functions of organs, tissues, and cells developed in xenogeneic chimeras are valuable for future translational research.

2. Trials of novel animal models

Gene knockout animals can easily be generated using genome editing systems such as the CRISPR/Cas system. Using the combination of this system and ESCs/iPSCs, complicated gene modification can be performed. We aim to produce novel animal models using these technologies.

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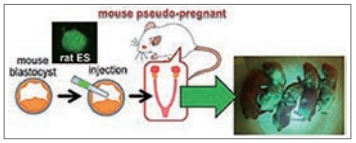

Fig. 1
Production of xenogeneic chimera
GPFP-expressing rat ES cells were in-jected into mouse blastocysts (mouse←rat ES chimera). We could obtain viable mouse←rat ES chimeras upon transplantation into the mouse uterus.

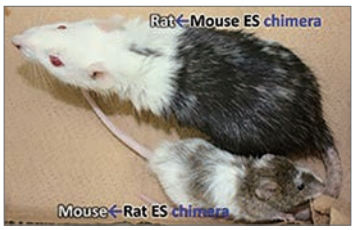

Fig. 2
Two kinds of mouse and rat xenogeneic chimeras
A rat-sized xenogeneic chimera which produced mouse ES cells injected into rat blastocysts (upper). A mouse-sized xenogeneic chimera which produced rat ES cells injected into mouse blastocysts (bottom).

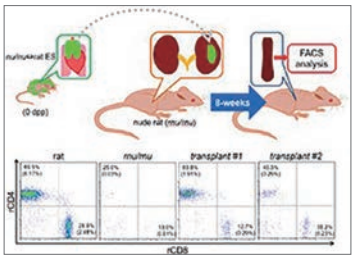

Fig. 3
The function of rat thymus in xenogeneic chimera
When rat thymus from a xenogeneic chimera was transplanted into renal subcutaneous tissues of nu/nu rat, rat T-cells were educated.

Cell Signaling

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Outline of Research and Education

Our research aims to elucidate intracellular signaling networks that sense and transmit diverse extracellular stimuli, with particular focus on the signaling pathways involved in cancerous cell proliferation and metabolic syndromes such as diabetes. To identify and analyze novel components of the signaling pathways, the studies utilize the fission yeast *Schizosaccharomyces pombe*, which has been successfully used as a genetically amenable model system to investigate cellular regulatory mechanisms conserved from yeast to humans. Students in our laboratory are encouraged to design multifaceted approaches that logically combine research tools in molecular genetics, cell biology and biochemistry. Originally established in 1998 at University of California-Davis, our laboratory has been training researchers that serve the international scientific community.

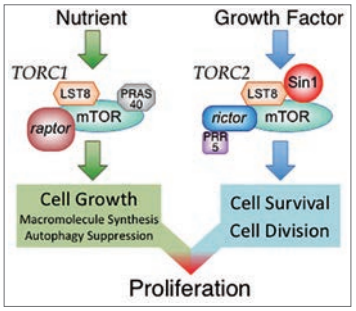

Fig. 1
The TORC1 and TORC2 signaling pathways integrate multiple stimuli to control cell proliferation.

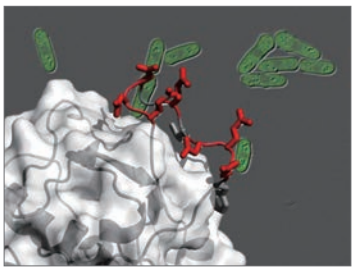

Fig. 2
The structure of the TORC2 subunit Sin1, whose function has been elucidated through genetic analysis in fission yeast (background).

Major Research Topics

1. TOR (Target Of Rapamycin) signaling pathways

TOR kinase forms two distinct protein complexes called TORC1 and TORC2, which mediate extracellular signals, such as nutrients and insulin/growth factors (Fig. 1). Deregulation of the TOR pathways is implicated in cancers, neurological disorders, diabetes and aging; therefore, comprehensive understanding of the TOR pathways is crucial for the development of informed strategies to treat these diseases.

2. Stress-responsive MAP kinase cascade

Stress-activated protein kinase (SAPK) is a member of the MAP kinase family that plays pivotal roles in cellular stress responses, including those of cancer cells exposed to cytotoxic therapies. Our goal is to discover cellular "stress sensors" that transmit signals to induce activation of SAPK.

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Applied Stress Microbiology


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Outline of Research and Education

Our research involves "Applied Molecular Microbiology". Our laboratory aims at basic studies in microbial science, particularly cellular response and adaptation to environmental stresses, and their biotechnological applications. We analyze and improve various functions of microorganisms at molecular, metabolic and cellular levels. As the best scenario, novel findings can be applied to the breeding of useful microbes (yeasts, bacteria), the production of valuable compounds (enzymes, amino acids) and the development of promising technologies (bioethanol, etc.).

Major Research Topics

1. Stress response and tolerance in yeast *Saccharomyces cerevisiae* (Figs. 1, 2, 3, 4)

We are interested in cellular response and adaptation to environmental stresses in the yeast Saccharomyces cerevisiae, which is an important microorganism as a model for higher eukaryotes. Yeast is also a useful microbe in the fermentation industry for the production of breads, alcoholic beverages and bioethanol. During fermentation, yeast cells are exposed to various stresses, including ethanol, high temperature, desiccation and osmotic pressure. Such stresses induce protein denaturation, reactive oxygen species generation, and lead to growth inhibition or cell death. In terms of application, stress tolerance is the key for yeast cells. We analyze the novel stress-tolerant mechanisms found in yeast listed below.

- Proline: physiological functions, metabolic regulation, transport mechanisms
- N-Acetyltransferase Mpr1: arginine biosynthesis, antioxidative mechanisms
- Nitric oxide (NO): synthetic mechanism, physiological roles
- Ubiquitin (Ub) system: protein quality control, Ub ligase Rsp5 regulation.

2. Development of industrial yeast based on novel stress-tolerant mechanisms

Through our basic research on novel stress-tolerant mechanisms, we construct industrial yeasts with higher fermentation ability under various stress conditions and contribute to yeast-based industries for the effective production of bread dough and alcoholic beverages, or breakthroughs in bioethanol production.

3. Endoplasmic reticulum (ER) stress and unfolded protein response (UPR)

We are pursuing the molecular mechanism by which ER stress triggers the UPR in yeast cells.

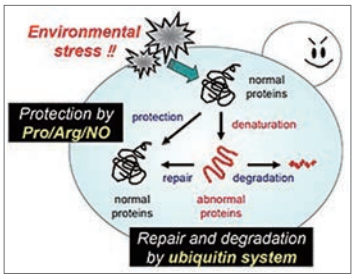

Fig. 1
Novel stress-tolerant mechanisms in *S. cerevisiae*

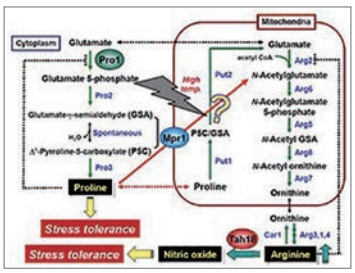

Fig. 2
Metabolic pathway of proline and arginine in *S. cerevisiae*

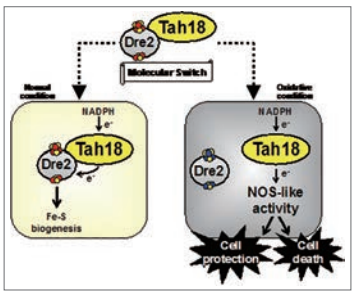

Fig. 3
Model of NO synthesis in *S. cerevisiae*

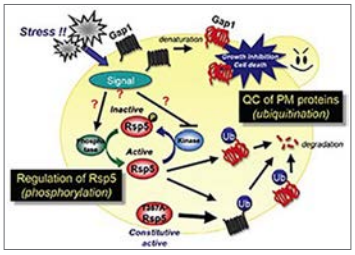

Fig. 4
Ubiquitin system under stress conditions in *S. cerevisiae*

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Environmental Microbiology

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Outline of Research and Education

Human beings have placed a heavy burden on the environment through modern mass production/consumption of petrochemical products which are not circulable. Microbes live in all environments and are deeply involved in the global homeostasis. Recently, we have discovered a microbe that degrades a plastic which was thought not to be biodegraded. Why do microbes possess such unique abilities? How did they attain them? To answer these questions, we study microbial molecules and assemblies. We believe that our studies will lead to solutions for the sustainable development of society.

Major Research Topics

1. Elucidation of a bacterial PET metabolism

Poly(ethylene terephthalate) (PET) is a material used for plastic bottles and polyester fibers. A bacterium that we discovered named *Ideonella sakaiensis* can degrade and metabolize PET. The fact that this bacterium nutritionally utilizes PET has been revealed through discoveries such as unique PET hydrolyzing enzymes. By unraveling bio-information such as genomes and transcriptomes and using genetic and biochemical methods, we aim to fully understand the molecular mechanisms involved in PET degradation.

2. Visualizing microbiology

Microbial research has been focused on analysis of cells that can be observed with an optical microscope, or molecules that can be followed by their presence such as enzymatic reactions. However, in recent years, it has been found that many microbes secrete much smaller structures than their cells. To open this new microbial world, we are trying to clarify the functions of these nanostructures using electron and super-resolution microscopes.

3. Plastic bioconversion

I. sakaiensis can eat PET. In other words, it has a metabolic system that can degrade and convert PET into energy and cellular components. We are attempting to breed the strains that produce high value compounds from waste PET products by modifying and/or enhancing their metabolism.

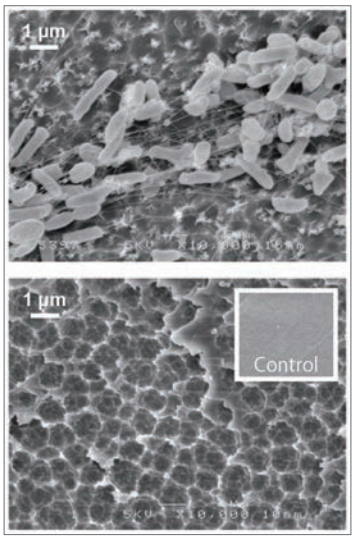

Fig. 1
A scanning electron microscopic image of *I. sakaiensis* cells grown on PET film (upper). The degraded PET film surface after washing out the adherent cells (lower).

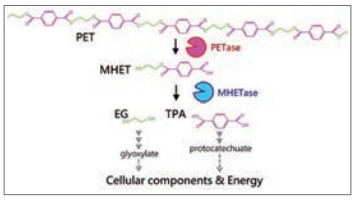

Fig. 2
Predicted PET metabolism by *I. sakaiensis*. Two unique enzymes, PET-ase and MHETase, are able to efficiently convert PET into its monomers.

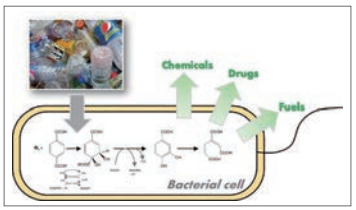

Fig. 3
Metabolic engineering to ferment waste plastic bottles into valued compounds.

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Structural Life Science

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Outline of Research and Education

In the cells, various proteins are involved in a variety of fundamental biological phenomena, especially motion. To understand life, it is crucial to know how these proteins function in the cell. Unfortunately, the molecular mechanisms of most of these proteins are still unclear. To unveil such mechanisms, our laboratory is working on various proteins. In particular, we are focusing on how proteins, small molecules, and ions are transported across membranes and how newly-synthesized proteins are folded into their functional states. This transportation and protein biogenesis are mediated by dedicated proteins including chaperones, proteases, transporters, channels, and translocases (Figs. 1, 2). Some of these membrane proteins can be drug targets. Also, there are proteins which drive the motility of the cell itself. Cilia and flagella are such organelles which are composed of over 600 kinds of proteins. To understand how these proteins work, it is crucial to know their detailed structures. Thus, our laboratory conducts fundamental research through structural biological analyses in combination with other newly developed methods.

The first step of our typical strategy is to elucidate the protein structure at the atomic and amino acid levels (Fig. 3). By obtaining detailed structural information of target proteins, much more insight into how these proteins function can be achieved. This is the greatest advantage of uncovering the details of protein structure. The next step is to reveal proposed molecular mechanisms based on protein's structural information by performing functional analyses. Recently, we are also attempting to visualize protein dynamics by single-molecule analyses. By utilizing several different methods for our research, our results provide new concepts that will change the contents of textbooks.

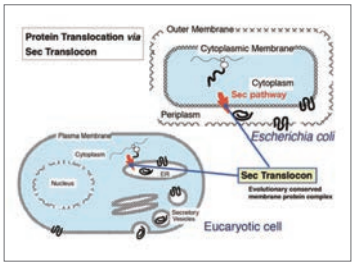

Fig. 1
Conserved protein translocation across the membrane via translocon.

Fig. 2
Membrane transporter

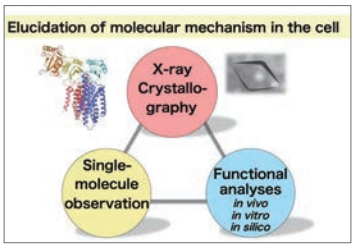

Fig. 3
Outline of our research

Major Research Topics

1. Transportation across cell membranes and protein biogenesis.

2. Molecular function and dynamics of proteins

3. X-ray crystallography and cryo-electron microscopy

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Gene Regulation Research



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Outline of Research and Education

Organisms are composed of various cells arranged in a well-coordinated manner. A fertilized egg repeats cell division and differentiates into the animal body in embryogenesis, in which various phenomena take place in a pre-determined order controlled by the inherent "biological clock" in each living body. We attempt to clarify the principles of animal morphogenesis through investigating the mechanisms of the "biological clock" that controls various life phenomena during embryonic development.

Major Research Topics

Research on somitogenesis in vertebrates as a model system for the biological clock

A mouse's body is composed of a metameric structure along the anteroposterior axis. For example, the spine is made up of the accumulation of multiple vertebrae, each of which is similar in shape. Such metamerism is based on the somite, which is a transient structure in mid-embryogenesis. Somites are symmetrically arranged on both sides of the neural tube as even-grained epithelial spheres that give rise to vertebrae, ribs, muscles and skin.

The primordium of the somite, located at the caudal tip of the mouse embryo, extends posteriorly. The anterior extremity of the somite primordium is pinched off to generate a pair of somites in a two-hour cycle, resulting in the formation of repeats of a similar size structure. On the basis of this finding, it has been considered that there is a biological clock, which determines the two-hour cycle, in the primordium of somites. The expression of several genes oscillates in the primordium of somites, corresponding to the cycle of somite segmentation, which serves as molecular evidence of the biological clock. We are exploring the mechanisms of the biological clock on the basis of such oscillatory gene expression.

Transcription factor Hes7 is specifically expressed in the primordium of somites (Fig. 1) and in a cyclic manner (Fig. 2). Through genetic and biochemical experiments, we have shown that Hes7 is involved as a principal factor in the mechanism for the biological clock that determines the two-hour cycle (Figs. 2, 3). We are conducting studies to understand the biological clock in a comprehensive manner.

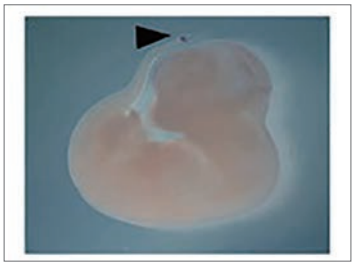

Fig. 1
Transcription factor Hes7, serving as a molecular clock, is specifically expressed in the primordium of somites.

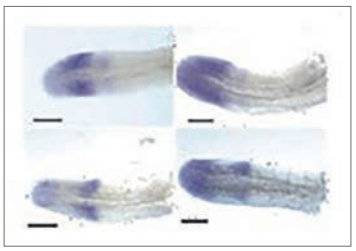

Fig. 2
The expression of Hes7 oscillates in the primordium of somites.

Fig. 3
In Hes7 knockout mice, somite segmentation does not occur cyclically and the metameric structures along the anteroposterior axis are lost.

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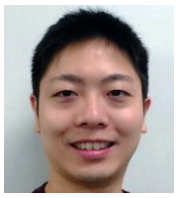
Systems Neurobiology and Medicine





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Assist. Prof. Kentarou Baba
Assist. Prof. Takunori Minegishi

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Outline of Research and Education

Neurons extend axons, and form elaborate networks in our brain; all the brain activities depend on neuronal networks. To establish proper neuronal networks, axons decide their migratory route in response to gradients of chemical signals in the brain. In addition to axons, various cells migrate within our body, thereby playing key roles in organ formation, immune responses, wound healing and regeneration. Disruption of axon guidance and cell migration is implicated in diseases, including birth abnormality, neuronal disabilities, immune disorders and cancer metastasis.

Our laboratory focuses on the proteins Shootin1a, Shootin1b and Singar, which we identified by proteome analyses, as well as their interacting proteins, Cortactin, L1-CAM and Rab33. We analyze the molecular mechanisms for axon formation, axon guidance, cell migration, and synaptic plasticity, using up-to-date methods including systems biology and mechanobiology. We also analyze actin waves, which is a new type of protein transport system for cell morphogenesis.

We expect that our studies will help us to understand the mechanisms underlying neuronal morphogenesis as well as the mechanisms underlying diseases including birth abnormality, neuronal disabilities, neuropsychiatric disorders and immune disorders, giving us a new window into therapeutic strategies for nerve injury, Alzheimer's disease, neuropsychiatric disorders and cancer metastasis.

Major Research Topics

1. Neuronal network formation: axon guidance and cell migration

2. Synaptic plasticity: learning and memory

3. Actin wave: a novel mechanism for intracellular protein transport

4. Research in medicine: brain diseases and cancer metastasis

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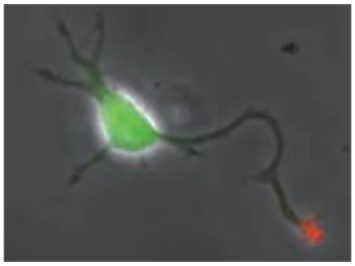


Fig. 1
Shootin1a (red) is a key molecule involved in axon formation and guidance [4, 5, 9, 10, 13, 15].

Fig. 2
Shootin1bb (magenta) is involved in neuronal migration [3, 7].

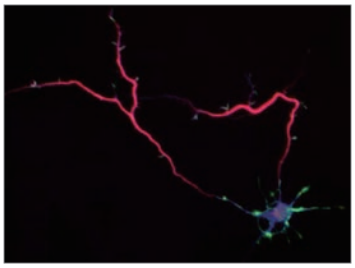


Fig. 3
Singar knockdown leads to formation of surplus axons [14].

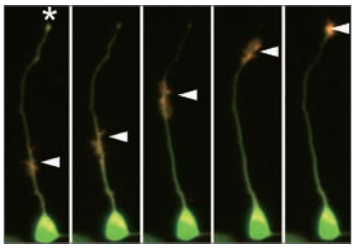


Fig. 4
Actin wave (arrow heads) migrating along an axon [6, 8]

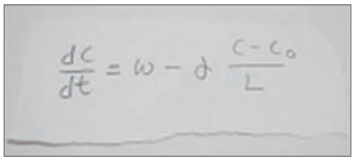
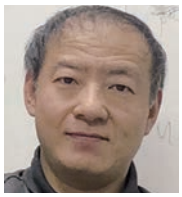


Fig. 5
An equation to describe shootin1a accumulation in axonal tip [12]

Computational Biology



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Outline of Research and Education

Our laboratory aims to extract the principle between biological molecules and target biological function and phenotype by computationally analyzing experimental data. We quantitatively associate molecules with function and phenotype to elucidate the underlying mechanism as a set of interactions among various physical quantities. Biological molecules and biochemical interactions actually play an important role in the regulation of biological function and phenotype. Many of functions and phenotypes are expressed in quantities different from molecular concentration, and some of them actively interacting with molecules. In other words, biological system functions as the interactions of multimodal quantities beyond the biochemistry! We aim to understand biological functions and phenotypes as aspects of the multimodal system. To achieve this goal, we collaborate with experimental researchers and analyze experimental data using mathematics and computer programs.

Major Research Topics

1. Systems biology on cell morphogenesis and migration (Fig. 1)
- System between morphogenesis and molecules regulating cytoskeleton formation and mechanical force
- Cell taxis depending on substratum stiffness
- Neuronal axon guidance depending on membrane potential

2. Systems biology on tissue formation (Fig. 2)
- Cell communication and synchronization for development of vertebrates
- Angiogenesis based on cell morphogenesis and migration
- Cross-scale analysis of organ size control

3. Application of machine learning and control theory to biological data (Fig. 3)
- Computer-assisted diagnosis using human breath gas.
- Estimation of essential kinases using inhibitor compounds.
- System identification of intracellular signal transduction with time-series analysis.
- System control of intracellular signal transduction with sequential Bayesian filter.
- Identification of intracellular molecular networks using multi-omics data.

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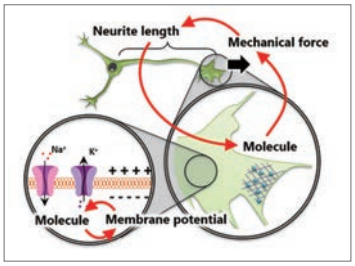

Fig. 1
Examples of system consisting of membrane potential and molecules, and system consisting of neurite length, mechanical force, and molecules. Signal transduction between various quantities are derived from experimental data. System can be reconstructed by integrating these signal transductions.

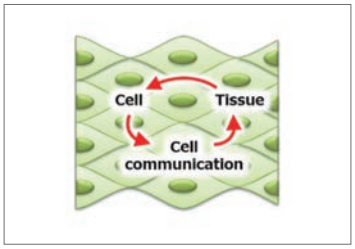

Fig. 2
Tissue formation can be regarded as the system consisting of cell, cell communication, and tissue itself. We aim to understand tissue formation as an aspect of such multimodal system.

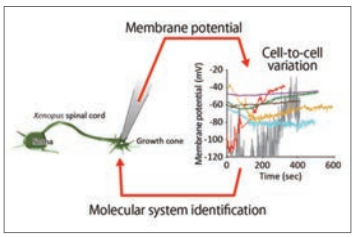

Fig. 3
Identification of molecular system from membrane potential time series. Measuring membrane potential is relatively easier than observing molecular interaction. Computation enables us to estimate intracellular molecular system from membrane potential.

Molecular Microbiology and Genetics
(with Research Institute of Innovative Technology for the Earth (RITE))

Prof.
Masayuki Inui

Lab page

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Outline of Research and Education

Global warming resulting from elevated CO_2 and global energy supply problems have been in the limelight in recent years. As these problems originate from rapid economic expansion and regional instability in parts of the world, broad knowledge of global economic systems as well as R&D is necessary to solve these problems. Fundamental research employing microbial functions to tackle the adverse effects of global climate change and mitigate energy supply problems is carried out in our laboratory.

Major Research Topics

1. Biorefinery

A biorefinery is the concept of production of chemicals and fuels from renewable biomass via biological processes. Biorefinery R&D is considered of national strategic importance in the U.S.A. (Fig. 1). A biorefinery can be divided into two processes: a saccharification process to hydrolyze biomass to sugars, and a bioconversion process to produce chemicals and fuels from the sugars. Based on a novel concept, we have pioneered a highly-efficient "growth-arrested bioprocess" as bioconversion technology to produce chemicals and fuels (Fig. 2). It is based on Corynebacteria that are widely used in industrial amino acid production. The key to high efficiency is the productivity of artificially growth-arrested microbial cells, cells with which we evaluate production of organic acids and biofuels. To efficiently produce these products, the cells are tailored for the production of a particular product using post genome technologies like transcriptomics, proteomics and metabolome analyses (Fig. 3).

2. Bioenergy and green chemicals production

Having established the fundamental technology to produce bioethanol from non-food biomass, we are now partnering with the automobile and petrochemical industries to explore commercial applications. We have also developed the platform technology to produce biobutanol, the expected next-generation biofuel, as well as a variety of green chemicals such as organic acids, alcohols and aromatic compounds from which diverse polymer raw materials used in various industries are produced.

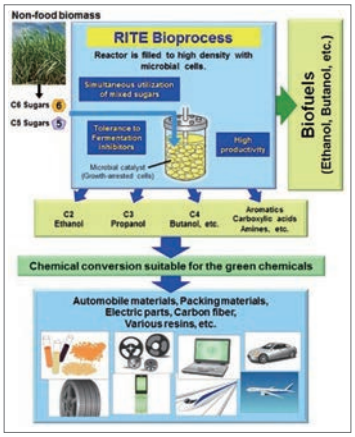

Fig. 1
The biorefinery concept

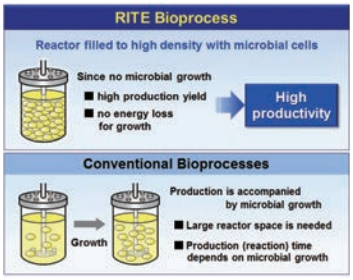

Fig. 2
Novel features of the RITE Bioprocess

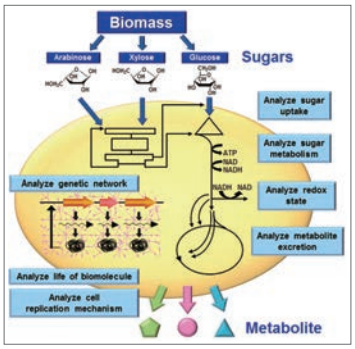

Fig. 3
Breeding of recombinant strains using system biology

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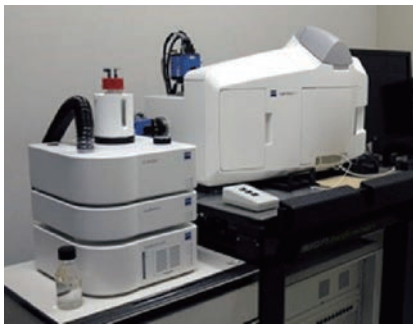
Abundant Research Facilities

Each division is equipped with a variety of state-of-the-art equipment.
Shared equipment, among the most advanced available for biological science research in Japan, is provided at numerous locations within the division.

Transmission Electron Microscope

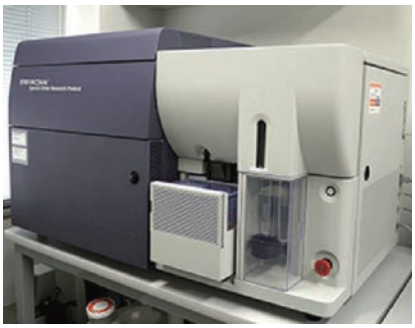
Scanning Electron Microscope

Confocal Laser Scanning Microscope

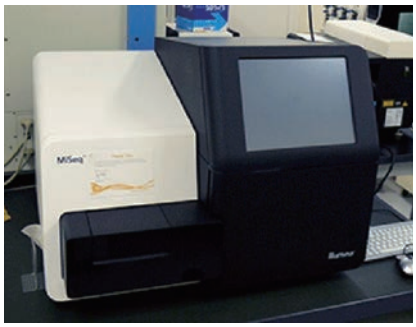


Light Sheet Fluorescence Microscope

High Resolution Fluorescence Microscopy Imaging System

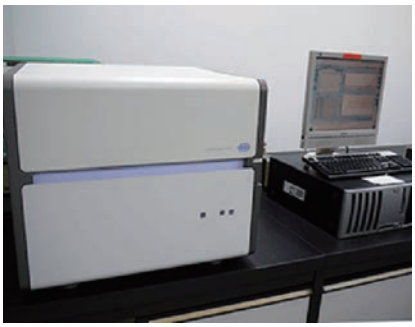


Flow Cytometer



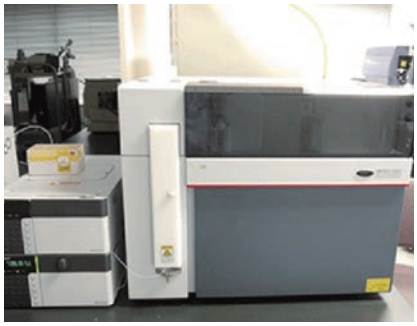
Next Generation Sequencer

DNA Sequencer



Real-Time PCR System

Triple Quadrupole Mass Spectrometer



Protein Sequencer

Micro Focus X-Ray CT System

Cell Preservation Containers

Botanical Greenhouses

Animal Experimentation Facility

Radioisotope Facility