Graduate School of
Biological Sciences

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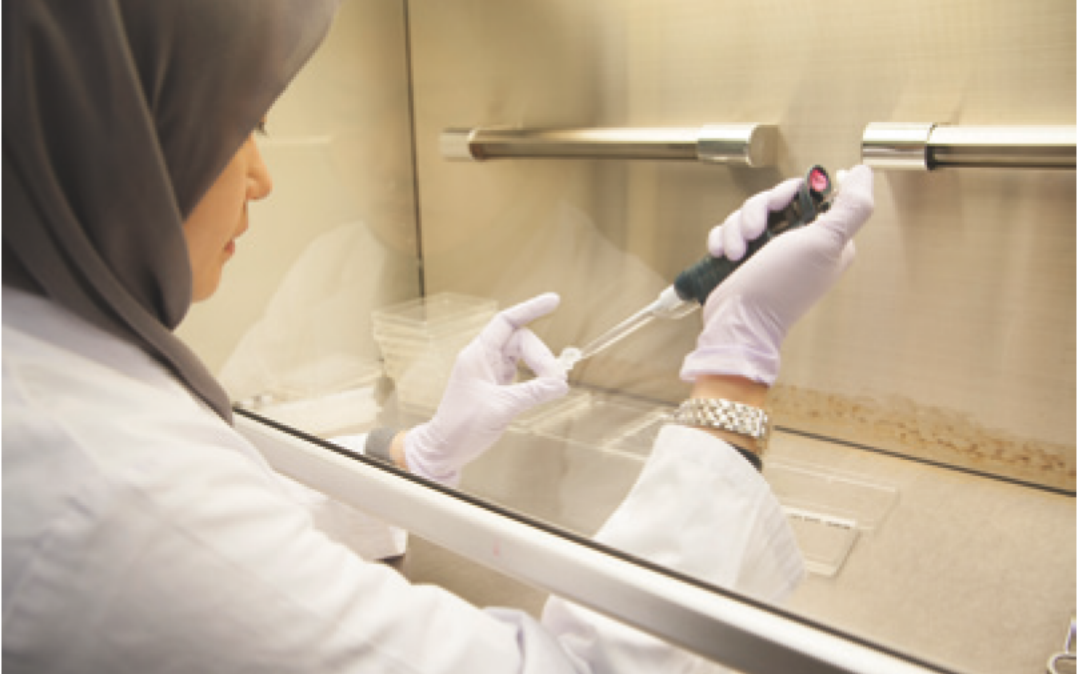
2015

Graduate School of Biological Sciences



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Introduction

to the Graduate School of

Biological Sciences

Looking at Cells from the Perspective of Molecules

The Graduate School of Biological Sciences undertakes advanced research to elucidate various structures and functions of microorganisms, plants and animals at the molecular and cellular levels, and clarifies principles of the basic phenomena of life and biological diversity.

In the 21st Century COE and the global COE programs, we elucidated the dynamic networks of molecules that comprise cells, using information science techniques in exhaustive analyses of genome sequences and protein structures. Based on such advanced fundamental research, the Graduate School of Biological Sciences produces research and development that benefits human well-being and trains researchers for active roles in the international community.

Active and high-level faculty and staff

Our dynamic research and education programs are led by internationally active faculty. The Graduate School of Biological Sciences is one of the top institutes in attracting funds such as Grants-in-Aid for scientific research and the COE programs from the Japan Society for the Promotion of Science and Japanese government ministries, showing that our faculty and staff are of high repute both inside and outside Japan.

Abundant research facilities

Each department is equipped with a variety of state-of-the-art equipment. Furthermore, shared equipment on a par with the most advanced available for biological science research in Japan is provided at numerous locations within the School.

Graduate school education with a comprehensive curriculum

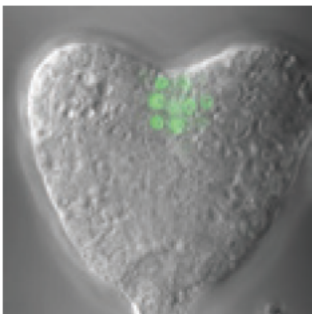
We provide two graduate courses to meet students' needs for their future careers: a two-year Bio-Expert course, and a five-year Frontier Bio course. We also offer an international masters course that is taught completely in English and a wide range of lectures covering the diverse fields of biological sciences.

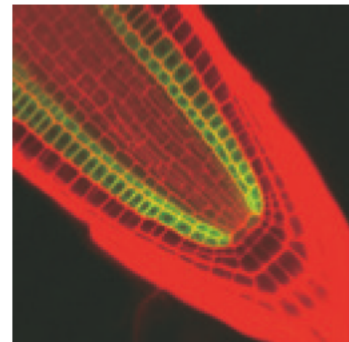
Support for student's research and life

We have a strong support system for students to enable them to engage in research without worrying about basic needs. We offer scholarships from the Japan Student Services Organization and other public and private entities, and TA and RA funds for distinguished students in the doctoral program.

New graduate university education system

NAIST's efforts to reform graduate university education have been recognized consecutively in programs promoted by MEXT: the Initiatives for Attractive Education in Graduate Schools (2005–2006), the Support Program for Improving Graduate School Education (2007–2009), and the Global Initiatives Program for Promoting Overseas Collaborative Research Toward Graduate Education in Biological Science, Nano-science, and Information Technology (2011-2016). With support from these programs, NAIST helps students to develop an autonomous and international outlook as part of a graduate university education that is unparalleled in Japan.





Research and Education Center for Genetic Information

We manage and operate campus-wide joint education and research facilities for radioisotope, animal and plant experiments at the Center. The Radioisotope Facility is responsible for the safety of radioisotopes used throughout NAIST as well as for user training. The Animal Experimentation Facility houses small animals and provides training for users. It also creates various transgenic mice to support research. The Botanical Greenhouses comprise both open and closed greenhouses. This facility houses the individual plants necessary for research activities, including transgenic plants.

These facilities are essential resources in advanced biological sciences. Technicians and other expert staff are employed to make sure the Center operates efficiently.

Graduate School of Biological Sciences

Departments & Faculty

Department of Plant Biology

Laboratory	Professor	Associate Professor	Assistant Professor
Intercellular Communications	Seiji Takayama		Yuko Wada, Kohji Murase, Sota Fujii
Plant Cell Function	Takashi Hashimoto	Tsubasa Shoji	Takehide Kato, Takashi Hotta
Plant Developmental Signaling	Keiji Nakajima		Shunsuke Miyashima
Plant Metabolic Regulation	Taku Demura		Ko Kato, Arata Yoneda, Misato Ohtani
Plant Growth Regulation	Masaaki Umeda		Yoko Okushima, Naoki Takahashi
Plant Morphological Dynamics	Masao Tasaka	Masahiko Furutani	Jun Itoh
Plant Immunity		Yusuke Saijo	Kei Hiruma
Plant Developmental Biology		Mitsuhiro Aida	

Department of Biomedical Science

Laboratory	Professor	Associate Professor	Assistant Professor
Molecular Signal Transduction	Hiroshi Itoh		Tetsuo Kobayashi, Noriko Kaji
Functional Neuroscience	Sadao Shiosaka	Shoji Komai	Hitomi Nakazawa
Gene Function in Animals	Masashi Kawaichi		Chio Oka, Eishou Matsuda
Functional Genomics and Medicine		Yasumasa Ishida	
Molecular and Cell Genetics	Kenji Kohno	Yukio Kimata	Akio Tsuru, Masaaki Koike
Tumor Cell Biology	Jun-ya Kato		Noriko Kato
Molecular Immunobiology		Taro Kawai	Takumi Kawasaki
Molecular Medicine and Cell Biology	Shiro Suetsugu		Kyoko Hanawa

Department of Systems Biology

Laboratory	Professor	Associate Professor	Assistant Professor
Microbial Molecular Genetics	Hisaji Maki	Masahiro Akiyama	Satoko Maki, Asako Furukohri
Systems Microbiology	Hirotada Mori		Ai Muto
Cell Signaling	Kaz Shiozaki		Hisashi Tatebe, Tomoyuki Fukuda
Applied Stress Microbiology	Hiroshi Takagi		Iwao Ohtsu, Daisuke Watanabe
Structural Biology	Toshio Hakoshima		Ken Kitano, Yoshinori Hirano
Membrane Molecular Biology		Tomoya Tsukazaki	Yoshiki Tanaka
Gene Regulation Research	Yasumasa Bessho		Takaaki Matsui, Yasukazu Nakahata, Takashi Akanuma
Systems Neurobiology and Medicine	Naoyuki Inagaki		Akihiro Urasaki

Plant Global Educational Project

Laboratory	Professor	Associate Professor	Assistant Professor
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Plant Advanced Research Project

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Affiliate Laboratories

Laboratory	Professor	Associate Professor
Molecular Genetics of Human Diseases (with Osaka Medical Center for Cancer and Cardiovascular Diseases)	Kikuya Kato	
Tissue Development Dynamics (with the Center for Developmental Biology, RIKEN)		Erina Kuranaga
Cell Growth Control (with the Center for Developmental Biology, RIKEN)		Takashi Nishimura
Molecular Microbiology and Genetics (with Research Institute of Innovative Technology for the Earth (RITE))	Masayuki Inui	

Laboratory Intercellular Communications

▶ URL: http://bsw3.naist.jp/eng/courses/courses102.html

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Outline of Research and Education

We are interested in studying the mechanisms of intercellular communication which are unique to plants. To answer the basic question of how plants recognize external signals and how these signals are transmitted into cells, we are conducting research to elucidate the molecular mechanisms of the following phenomena.

Major Research Topics

1. Mechanisms of self-incompatibility in plants

Self-incompatibility (SI) is a genetic system used by many flowering plants to prevent self-fertilization and thereby generate and maintain genetic diversities within the species. Our laboratory has been studying the molecular mechanisms of SI in plants of the Brassicaceae and Solanaceae families. Molecular mechanisms for plant sexual reproduction process.

We found that self/non-self recognition in the Brassicaceae is mediated by the direct interaction between pollen ligand and pistil receptor kinase (Fig. 1). Currently, we are working to elucidate the downstream signaling cascade leading to the rejection of self-pollen. The downstream events of SI (incompatible pathway) would be to interrupt the events that promote successful pollen germination and tube growth (compatible pathway). Thus, we are also working to identify the key components at work in this compatible pathway by using Arabidopsis thaliana, a self-compatible model plant in the Brassicaceae.

For SI in the Solanaceae and Rosaceae families, we have proposed a model in which cytotoxic pistil ribonuclease is specifically degraded through proteasome pathway in non-self pollen tubes. Recently, we found that pollen elements are multiple F-box proteins that are expected to collaboratively detoxify non-self ribonucleases. We are now testing the validity of this model (Fig. 2).

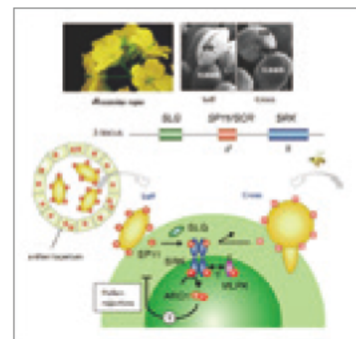

Fig.1 Mechanism for self-incompatibility in the Brassicaceae

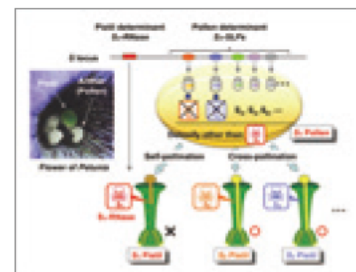

Fig.2 Mechanism for self-incompatibility in the Solanaceae

2. Mechanisms of monoallelic gene expression in plants

A diploid organism has two copies of each genes, one inherited from each parent. Although the majority of genes is expressed equally from both alleles, recent studies suggest that lots of genes frequently show monoallelic expression, although the underlying molecular mechanisms are unknown. These widespread monoallelic expressions receive much attention because they affect diversity in gene expression and phenotypic variation and onset of disease.

While studying dominant/recessive relationships between self-incompatibility genes, we found that the expression of recessive alleles was suppressed by small RNA derived from dominant alleles. We are now conducting studies to further clarify the mechanism of this epigenetic monoallelic expression system (Fig. 3).

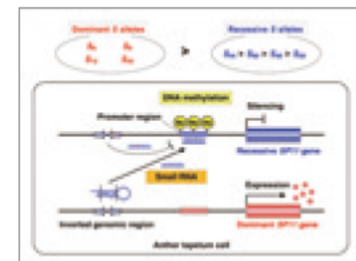

Fig.3 Models for epigenetic control of dominant/recessive relationship

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Laboratory Plant Cell Function

▶ URL: http://bsw3.naist.jp/eng/courses/courses103.html

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Outline of Research and Education

We conduct extensive research, from basic to applied, concerning the cellular function, signal transduction and regulation of gene expression in higher-plants, making effective use of molecular genetics and imaging technologies on Arabidopsis thaliana, tobacco, and tomatoes.

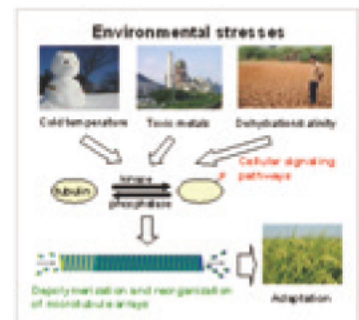

Fig.1 Environmental stresses remodel the microtubule cytoskeleton by phosphorylation of tubulin subunits.

Major Research Topics

1. Dynamic reorganization of microtubule cytoskeletons in response to environmental stimuli and during plant growth

- Pattern formation of bio-polymer networks
- Regulators of microtubule dynamics
- Left-right asymmetry establishment in cell shape
- Stress-induced reorganization of microtubule arrays

2. Biosynthesis of bio-active natural products

- Enzymes and transporters for nicotine in tobacco
- Herbivory activation of wound-signaling pathways for defense compound biosynthesis
- Novel natural products in crop plants

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

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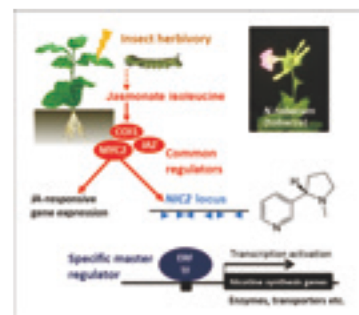

Fig.3 Jasmonate-responsive ERF transcription factor genes clustered at NIC2 locus regulate nicotine biosynthesis in tobacco.

Laboratory

Plant Developmental Signaling

▶ URL: http://bsw3.naist.jp/eng/courses/courses110.html

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Outline of Research and Education

Microscopic observation of plant sections allows one to realize the beautiful patterns of cells, each with a different shape and size (Fig.1). These cells are not only diverse in appearance, but are functionally specialized to play specific roles in each organ. These tissue patterns are produced from a single cell, the zygote. One of the most fundamental questions in plant developmental biology is how complex plant structures are derived from a single cell.

Our research group is trying to identify basic principles of plant development using model plant species. We aim to understand the intercellular signal transduction pathways underlying the pattern formation of roots and embryos, as well as cell reprogramming that triggers embryogenesis.

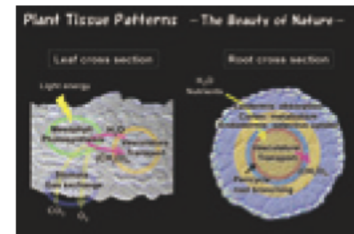

Fig.1 (Left) In leaves, specialized cell types such as mesophyll, stomata, and vascular cells, are spatially arranged to maximize photosynthetic ability. (Right) Root tissues are organized into a concentric pattern that facilitates water and nutrient uptake, as well as their metabolism and translocation.

Major Research Topics

1. Cell-cell communication in tissue patterning

Due to the presence of rigid cell walls, plant cells are generally unable to alter their direction or position in the organ primordia. Therefore, timing and orientation of cell divisions, as well as cell fates, are determined by interpreting the positional cues of surrounding cells. Such developmental mechanisms rely on the presence of intimate cell-cell communication pathways. Our recent studies revealed the presence of novel signaling pathways that allow regulatory molecules such as transcription factors and microRNAs to traffic from cell to cell (Fig.2). We are currently focusing on the molecular mechanisms that allow microRNAs to move from cell to cell, as well as the evolution of such pathways.

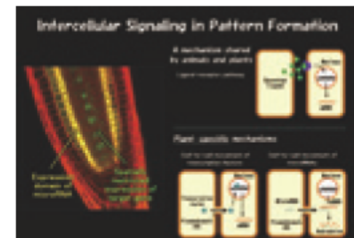

Fig.2 Plant cells are connected with a cytoplasmic continuum termed the plasmodesmata (PD). PD allows passage of regulatory molecules, such as transcription factors and small RNAs, thereby serving as a channel to transmit developmental signals.

2. Cell reprogramming and pattern formation during embryogenesis

Embryogenesis of the Brassica family, including the model plant Arabidopsis, proceeds in a highly coordinated manner (Fig.3). Similar to innovation of iPS cells, activation of an embryo-specific developmental program is initiated only after the reprogramming of somatic cells into the embryonic status. We have recently discovered a key reprogramming factor in Arabidopsis, and are currently investigating its mechanism of action. We are also constructing a translational approach that utilizes this reprogramming factor to propagate useful plant lines without waiting for the transition to the reproductive growth phase.

Fig.3 Pattern formation in embryogenesis is triggered by cell reprogramming and proceeds in a highly ordered manner. We are studying the mechanisms underlying embryonic pattern formation and reprogramming, as well as application of the reprogramming factor for efficient propagation of useful plants.

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Laboratory Plant Metabolic Regulation

► URL: http://bsw3.naist.jp/eng/courses/courses104.html

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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, the environment, and energy. Based on omics technologies, we are clarifying the mechanisms for gene expression regulation for woody cell differentiation, to develop novel biotechnological tools leading to the establishment of a sustainable society.

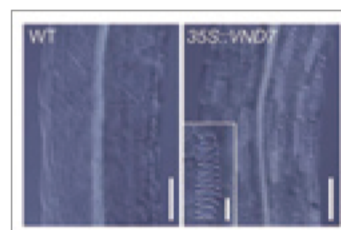

Fig.1 VND7 acts as a key regulator of the xylem vessel differentiation. Overexpression of VND7 induces transdifferentiation of epidermal cells into xylem vessel elements with spiral structure of secondary wall thickening (arrows) in hypocotyle. Bar=100 μm.

Major Research Topics

1. Analysis of molecular mechanisms governing xylem cell differentiation

2. Molecular and cell biological approaches to trees

3. Highly-efficient transgene expression systems of higher plants

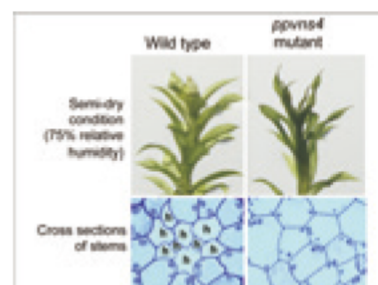

Fig.2 Moss *Physcomitrella patens ppvns* mutants, a knock out mutant for one of VND-homologous genes, showed the malformation of hydroids (h) in stems, thus leading to the decreased water transport activity accompanied with the wilting phenotype under semi-dry condition.

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Laboratory

Plant Growth Regulation

▶ URL: http://bsw3.naist.jp/eng/courses/courses105.html

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Outline of Research and Education

Because plant cells are surrounded by a rigid cell wall, they cannot - unlike animal cells - move within organs. Therefore, plants control cell division in a precise, spatiotemporal manner to achieve proper development of organs. However, little is known about how the cell cycle is regulated during morphogenesis and under various environmental conditions. We focus on the molecular mechanisms underlying cell cycle control in response to internal and external signals, such as phytohormones and environmental stresses. Our studies will broaden the understanding of plant survival strategies, and provide insights into molecular breeding to yield an increase of plant biomass.

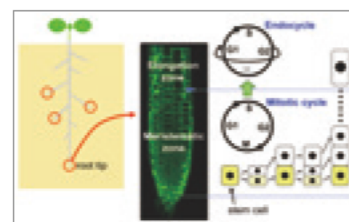

Fig.1 Cell cycle regulation in root growth

Major Research Topics

1. Regulation of cell division, cell growth and genome stability during plant development (Fig.1)

- Cell cycle control by auxin and cytokinin
- Cell cycle time-lapse imaging in different cell types
- DNA damage signaling mediated by transcription factor SOG1
- Crosstalk between DNA damage and defense responses

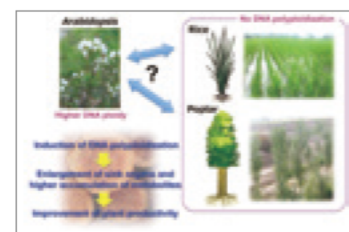

Fig.2 Development of high-biomass plants by induction of DNA polyploidization

2. Developing technologies for plant productivity improvement by inducing DNA polyploidization (Fig.2)

- Epigenetic control of induction of DNA polyploidization
- Improvement of biomass productivity in poplars

3. Control of cell division and organ size by fatty acid-derived signals from the epidermis (Fig.3)

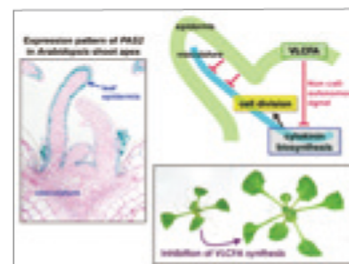

Fig.3 Epidermis-derived signals control organ size. VLCFA, very-long-chain fatty acids; *PAS2, PASTICCINO2*

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Laboratory Plant Morphological Dynamics

▶ URL: http://bsw3.naist.jp/eng/courses/courses105.html

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Outline of Research and Education

During embryogenesis in higher plants, special tissues called the shoot and root meristems are formed at the upper and lower ends, respectively. After germination, the shoot meristem forms above-ground organs such as leaves, stems and floral organs, while the root meristem produces underground roots. Both genetic controls and diverse external environmental factors such as light or gravity influence the formation of the plant body. By using Arabidopsis thaliana, a model crucifer plant suitable for molecular genetic analyses, we study the molecular mechanisms that regulate plant development.

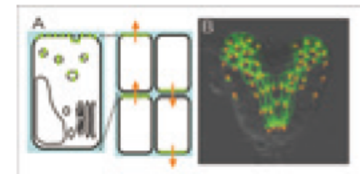

Fig.1 (A) Auxin efflux carriers (green) are localized in the plasma membrane with polarity and auxin is transported to a neighboring cell (orange arrow). (B) Localization of GFP-tagged auxin efflux carrier (green) and presumptive auxin flows (orange arrows) in Arabidopsisembryo

Major Research Topics

1. Polar auxin transport mechanisms

2. Molecular mechanisms for auxin-dependent gene transcription

3. Molecular mechanisms for secondary growth

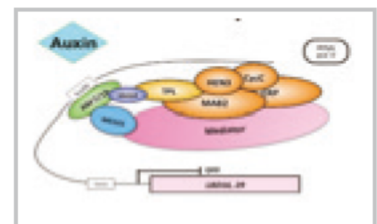

Fig.2 A schematic diagram of auxin-dependent transcription: The transcription factor AUXIN RESPONSE FACTOR (ARF) binds to an auxin-responsive element AuxRE in the promoter region of target genes. A mediator complex transmits information from the ARF to RNA polymerase II.

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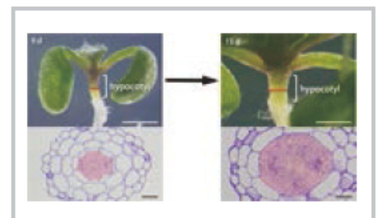

Fig.3 Secondary growth in Arabidopsis hypocotyl. Arabidopsis hypocotyl undergoes substantial secondary growth in the stele (red circled area) as a result of the activities of the vascular cambium and the cork cambium.

Laboratory

Plant Immunity

▶ URL: http://bsw3.naist.jp/eng/courses/courses111.html

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Outline of Research and Education

In nature, plants cope with a wide range of microbes that reside on the surface of or within plant tissues. Plants disregard or tolerate the presence of these plant-inhabiting microbes at non-damaging levels, despite an elaborate innate immune system to detect and repel microbes. We hypothesize that plant immunity senses and reacts to "danger" signals (DAMPs) generated upon pathogen challenges over the background microbial signals (MAMPs). We aim to decipher the molecular principles and mechanisms underlying this sophisticated function of plant immunity, with major focuses on immune sensors and signaling, defense-related transcriptional reprogramming, and microbial strategies to avoid/dampen host immune activation. We believe that our studies will give important insight into general principles of plant immunity, and thus offer new effective approaches for controlling plant health and growth in sustainable agriculture.

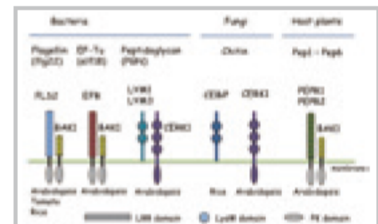

Fig.1 Pattern recognition receptors and co-receptors in plants

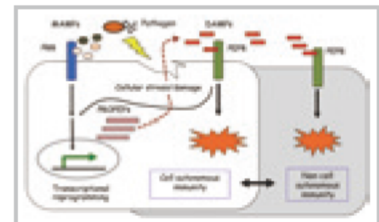

Fig.2 Layered MAMP- and DAMP-receptor signaling confers robustness to plant immunity.

Major Research Topics

1. Pattern-triggered immunity upon sensing microbe- or danger-associated signals

2. Transcriptional reprogramming and priming in plant immunity

3. Signal integration between biotic and abiotic stress responses

4. Endophytic and pathogenic microbes in plants

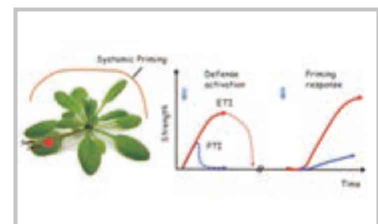

Fig.3 Transcriptional reprogramming and priming in plant immunity. Following the initial defense activation (left arrow) upon recognition of pathogen-associated patterns(PTI) or effectors(ETI), defense-related genes become primed to allow faster and/or greater responses upon second stimulation (right arrow). Histone modifications provide a basis for this immune memory that can be inherited by the next generation.

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Laboratory Plant Developmental Biology

▶ URL: http://bsw3.naist.jp/eng/courses/courses108.html

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Outline of Research and Education

Why can plants continuously grow upwards throughout their lifetime? How do plant organs such as leaves and floral organs acquire the diverse shapes that we see around us? To answer these questions, we focus on a small tissue called the shoot meristem, which is located at the tip of the stem (Fig.1). The shoot meristem contains a group of undifferentiated cells in its center. These cells proliferate to produce differentiated organs while they renew themselves to maintain their entity. Cells in the meristem thus possess characteristics of "stem cells", representing a common strategy for generating complex structures in multicellular organisms. The self-maintaining ability of the meristem is remarkable: in some species, its activity can last for more than a thousand years to produce a tall tree that reaches 100 meters in height. The activity of the shoot meristem is modified upon developmental and environmental cues so that it can produce appropriate types of organs with different shapes. The aim of our research is to understand molecular and cellular mechanisms that control the activity of this fascinating tissue, using the model plant *Arabidopsis thaliana*.

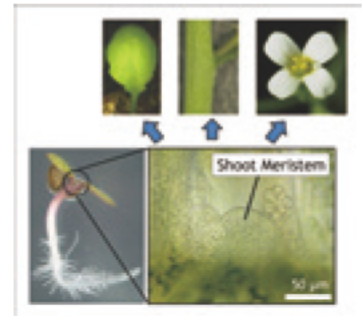

Fig.1 Shoot meristem is the source of most aerial organs, such as leaves, stems and flowers.

Major Research Topics

1. Shoot meristem establishment during embryogenesis

2. Flower development and meristem activity

3. Specification and morphogenesis of carpels

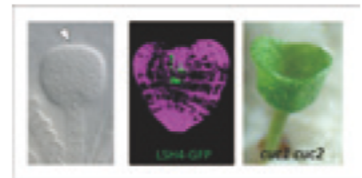

Fig.2 Left: *Arabidopsis* embryo at the globular stage: The arrowhead indicates the site of shoot meristem formation.
Center: Localization of a protein (green) encoded by one of the CUC1 and CUC2 downstream genes in the heat stage embryo
Right: A mutant that lacks both CUC1 and CUC2 activity: Cotyledons are fused and no shoot meristem is formed.

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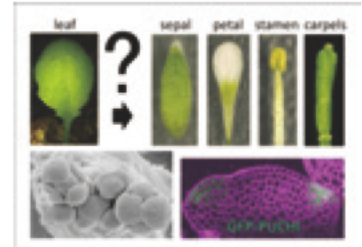

Fig.3 Top: Although homeotic genes are known to convert a leaf into any of the floral organs, how they do this is still largely unknown.
Bottom left: The shoot meristem (central dome) produces floral meristems.
Bottom right: PUCHI protein (green) marks two early flower primordia successively produced from the shoot meristem.

Laboratory

Molecular Signal Transduction

▶ URL: http://bsw3.naist.jp/eng/courses/courses202.html

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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. Many drugs targeted at the 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.

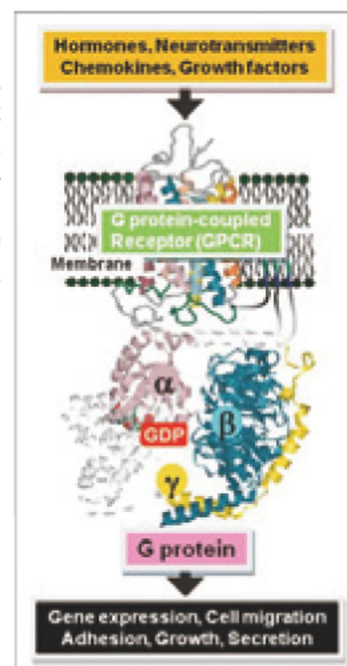

Fig.1 Signal transduction mediated by G protein-coupled receptor

Major Research Topics

1. Cellular functions and regulatory mechanisms of G protein signaling

2. Molecular mechanisms of self-renewal, differentiation, and migration of neural stem cells

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

4. Regulation of primary cilia formation and function in mammalian cells

5. Molecular mechanisms of epithelial morphogenesis and cancer

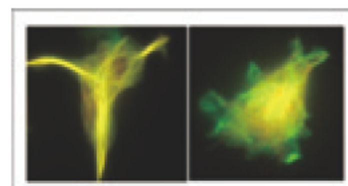

Fig.2 G protein/PKA signal-regulated dynamics of cytoskeleton in neuronal progenitor cells

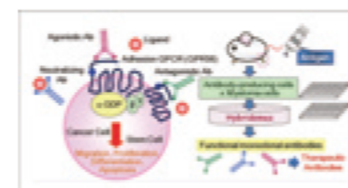

Fig.3 Monoclonal antibody against orphan GPCR as a tool for signal analysis

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Laboratory Functional Neuroscience

▶ URL: http://bsw3.naist.jp/eng/courses/courses205.html

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Outline of Research and Education

1. Our current research and education are focused on the neural functions of the hippocampus, amygdala, and prefrontal cortex using techniques of neuroanatomy, electrophysiology, biochemistry and behavioral neuroscience. Major topics are:
- the mechanisms of structural plasticity in the neuronal circuits for memory and learning
- a mechanism for signal transduction in the limbic system
- a mechanism for synaptic tagging through molecular based studies of synaptic potentiation and efficiency control

2. To study the neural activity and the neuronal plasticity observed during animal behaviors depending on its experiences, it is necessary to perform multi-faceted research covering extensive fields, ranging from molecules to behaviors. In our laboratory, we are attempting to achieve this goal by taking single-cell recordings from the brains of animals while performing an activity, making use of patch clamping in vivo.

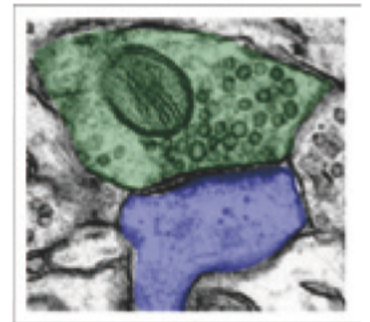

Fig.1 Electron microscopic profile of a synapse in the hippocampal pyramidal layer: The presynapse is colored green and the postsynapse is blue.

Major Research Topics

The synaptic contacts are composed of cell adhesion and extracellular matrix molecules (CAMs and ECMs) which are sensitive to intracellular and extracellular signaling. It has been unveiled that proteases cleave CAMs and ECMs and the cleaving process might regulate the synaptic potentiation relating cortical and limbic brain functions. In our laboratory, several novel secretory-type serine proteases were cloned and we have analyzed their functions in detail. To date, we have demonstrated that neuropsin (also referred to as klk8) plays a significant role in the regulation of the early phase of long-term potentiation (E-LTP), and regulates intracellular signals of the limbic brain.

However, there are many unresolved questions over how this protease affects the signals from the outside to the inside of the cells and how it regulates the synaptic function via proteolysis processing. Moreover, it is unknown what roles this mechanism plays in acquisition and/or retention of memories. Our research is currently in progress to resolve these questions concerning the molecular mechanisms of behavioral memory.

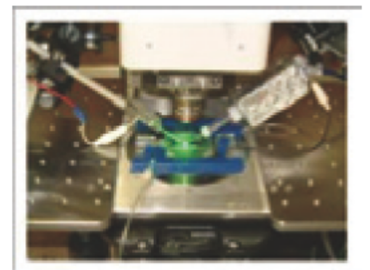

Fig.2 Electrophysiological analysis of synaptic functions: Electrodes are inserted into a hippocampal slice and membrane currents or potentials are recorded.

Fig.3 Behavioral analysis of memory and learning: Animals (mice) are given various learning tasks and the course of their learning is observed in detail.

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Laboratory

Gene Function in Animals

▶ URL: http://bsw3.naist.jp/eng/courses/courses206.html

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Outline of Research and Education

Many human diseases are caused by disturbances in gene function and expression. Understanding of gene function and the mode of regulation is important in developing new cures for diseases. We identify and analyze genes involved in the onset of human diseases, and are especially interested in diseases closely related to human aging processes.

Furthermore, in view of the post-genomic age, we develop new techniques that enable rapid and systematic analysis of animal gene function. To this end, we are constructing an ES cell library in which one of every mouse gene is disrupted in each ES cell clone by randomized insertion of retrovirus or transposon DNA. We conduct research on one particular gene isolated by this technique. This gene encodes a novel methyl DNA binding protein and is involved in epigenetic control of various aspects of human development by regulating cell death, proliferation, and differentiation.

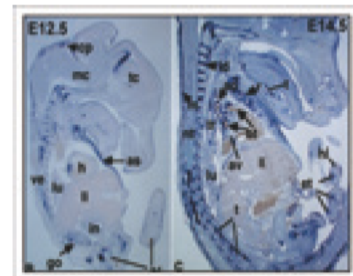

Fig.1 HtrA1 gene involved in the onset of arthritis is primarily expressed in the skeletal system of mouse fetuses and regulates the differentiation of cells in cartilage and bone.

Major Research Topics

1. Research on genes of the HtrA serine protease family which are involved in the onset of osteoarthritis, age-related macular degeneration, familiar brain infarction, preeclampsia and tumorigenesis (Fig.1)
2. Analysis of Atcay family proteins, Atcay and BNIP-2, which bridge kinesin-1 and its vesicular cargos such as mitochondria and are involved in intracellular trafficking. Deficiency of Atcay causes the human hereditary disease called Cayman type cerebellar ataxia.
3. Development and application of the gene trap technique which enables efficient, random, and conditional disruption of every mouse gene in ES cells by using unique features of transposons (Fig.2)
4. Functional analysis of a methylated DNA binding transcription factor, CIBZ, with regard to the regulation of cell differentiation, proliferation, programmed cell death and carcinogenesis (Fig.3)

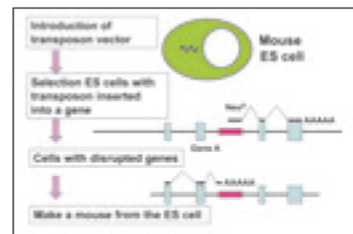

Fig.2 Gene trap technique: Every gene in the mouse ES cell is randomly disrupted by insertion of transposon DNA. The phonotype of the mouse produced from the ES cell will be analyzed to reveal the function of the gene.

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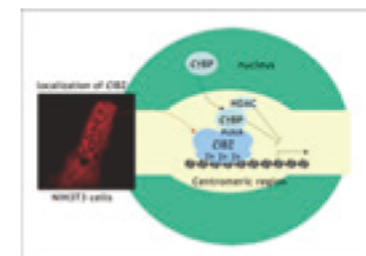

Fig.3 CIBZ suppresses transcription by recruiting CtBP (a transcription suppression cofactor used commonly for various transcription suppressing mechanisms) and histone deacetylase to the heterochromatic area of the centromere.

Laboratory Functional Genomics and Medicine

▶ URL: http://bsw3.naist.jp/eng/courses/courses211.html

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Outline of Research and Education

Upon completion of sequencing the genomes of a variety of organisms including the mouse and human being, it became our big task to elucidate the functions of the sequenced genomes. For this purpose, some biomedical researchers inactivate particular genes of their interest in the mouse and analyze the phenotypes of the mutated animals, thereby revealing the functions of the inactivated genes. Our research group develops novel strategies of random insertional mutagenesis of mouse embryonic stem (ES) cells. Also, we investigate the molecular mechanisms commonly involved in translation termination and an mRNA-surveillance function called nonsense-mediated mRNA decay (NMD) in mammalian cells.

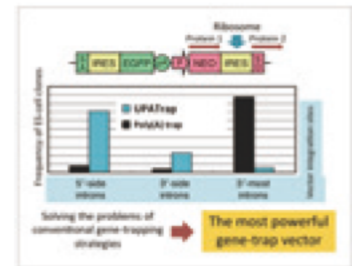

Fig.1 The UPATrap method for the random insertional mutagenesis of transcriptionally silent genes in target cells.

Major Research Topics

1. Development of novel gene-trapping strategies

Previously, it was almost impossible to inactivate transcriptionally silent genes in ES cells by random gene trapping. Almost 10 years ago, we developed a novel gene-trapping strategy termed UPATrap based on the suppression of NMD, thus allowing such difficult gene disruption for the first time (Fig. 1). We are going to upgrade the UPATrap technology in order to randomly disrupt long non-coding mRNA genes as well as protein-coding ones. We also produce mutant mice using newly developed techniques and analyze their phenotypes.

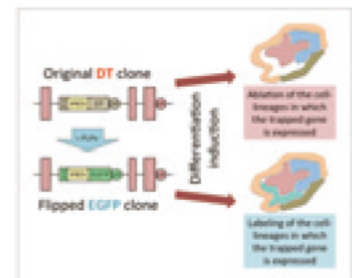

Fig.2 A novel gene-trapping strategy with the use of the DT cytotoxicity and cell-lineage ablation.

2. Cell-lineage ablation in the mouse

For the selective inactivation of transcriptionally silent genes in ES cells, we developed a novel gene-trapping strategy utilizing the strong cytotoxic activity of the diphtheria toxin (DT). In addition to the inactivation of trapped genes, it is also possible to attain ablation of cell-lineages in which the trapped genes are expressed (Fig. 2). We analyze the mice that have had particular cell-lineages removed, thereby elucidating the physiological roles of the ablated cell populations.

3. On translation termination in mammalian cells

As molecular mechanisms involved in protein synthesis in mammalian cells, translation initiation and elongation reactions have already been well-characterized, but translation termination still has much to be investigated. We have proposed the "reeling-in" model of the 3-prime untranslated region of an mRNA that should be able to explain the common molecular mechanisms shared between translation termination and NMD (Fig. 3). We will test stringently whether this model is really valid or not.

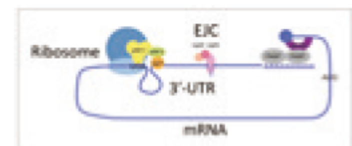

Fig.3 The "reeling-in" model of protein translation termination in mammalian cells.

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Laboratory Molecular and Cell Genetics

▶ URL: http://bsw3.naist.jp/eng/courses/courses207.html

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Outline of Research and Education

The endoplasmic reticulum (ER) is an important organelle in which newly synthesized secretory and membrane proteins are correctly folded and assembled. We are conducting the following studies: the signal transduction pathways (UPR: unfolded protein response) from the ER to the cytosol/nucleus, the quality control of protein folding in the ER, and the physiological roles of UPR at the molecular, cellular, and individual animal levels. We are also interested in the study of diseases caused by UPR dysfunction.

In our other work, we have developed a simple and highly sensitive method for conditional cell ablation in transgenic mice, called "toxin receptor-mediated cell knockout (TRECK)". We have created mouse models of hepatitis and diabetes mellitus and are conducting studies on regenerative medicine by using these TRECK-Tg mice.

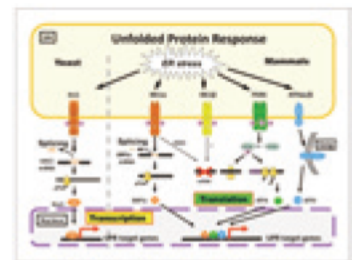

Fig.1 Unfolded Protein Response in yeast and mammals

Major Research Topics

1. ER quality control and Unfolded Protein Response (UPR)

- ER stress-sensing mechanism by IRE1
- Molecular analysis of unconventional splicing in mammals
- Physiological functions of IRE1α and IRE1β using KO mice
- Analysis of a novel ER chaperone molecule DNAJB12

2. Regenerative medicine using TRECK-Tg mice

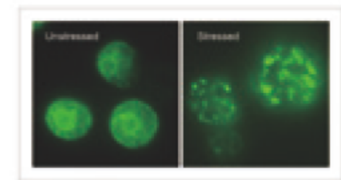

Fig.2 Cluster formation (right) of yeast IRE1 under ER stress

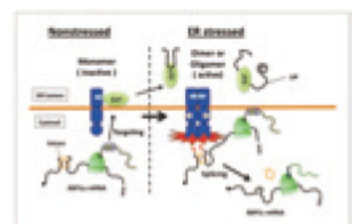

Fig.3 Unconventional splicing of *XBP1* mRNA in mammalian IRE1α -XBP1 pathway

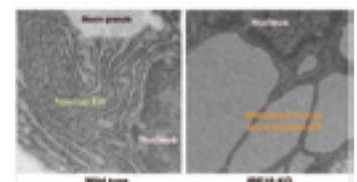
Fig.4 The ER in IRE1β KO goblet cells is distended with misfolded mucin accumulation

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Laboratory Tumor Cell Biology

▶ URL: http://bsw3.naist.jp/eng/courses/courses208.html

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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. The findings can be applied to regenerative medicine and cancer research. We use the following experimental systems:

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

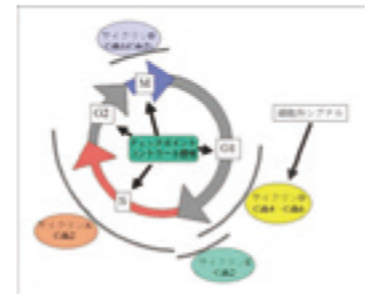

Fig.1 Cell cycle and cyclin/Cdk complexes

Major Research Topics

1. Cell cycle control and oncogenesis

・Cell cycle control and oncogenesis: During the cell cycle, the decision on whether cells should proliferate or stop growing and prepare for differentiation is determined at the G1 phase. Therefore, we investigate the function of molecules that promote or inhibit the progression of 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 are analyzing the key molecules involved in cell proliferation, G1 regulation, and checkpoint control, and investigating the mechanisms involved in the abnormal growth of cells and cellular oncogenesis.

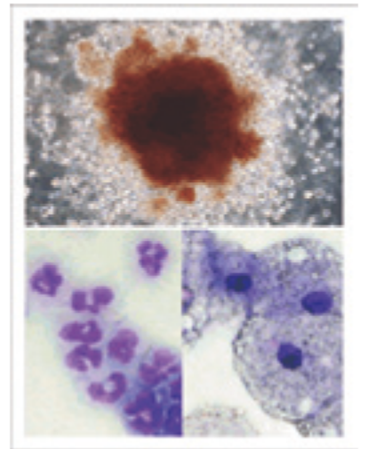

Fig.2 A group of erythrocytes and leukocytes (upper), neutrophils (lower left) and macrophages (lower right), which were induced to differentiate from ES cells in vitro

2. Leukemogenesis

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

3. Hematopoietic stem cells

We are performing studies on hematopoietic stem cells, present in the bone marrow. We are aiming to develop 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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Laboratory

Molecular Immunobiology

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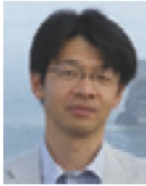

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Outline of Research and Education

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 tightly 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.

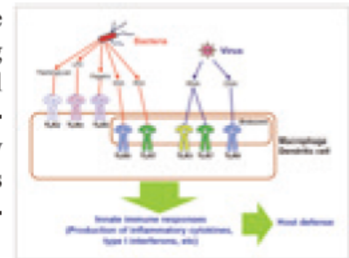

Fig.1 Recognition of microbial components by Toll-like receptors (TLRs)

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.

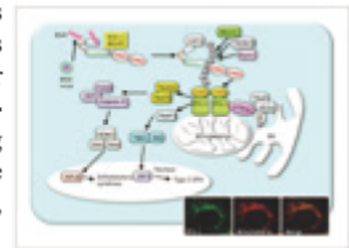

Fig.2 Signaling pathways through RLRs, cytosolic sensors for RNA viruses

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

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Laboratory Molecular Medicine and Cell Biology

▶ URL: http://bsw3.naist.jp/eng/courses/courses210.html

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Outline of Research and Education

Each type of cell has a specific shape that is determined by the plasma membrane. The shape of the plasma membrane is determined by the support of the cytoskeleton. Our lab focuses on the mechanisms connecting the membrane to the cytoskeleton, and the consequences of cellular signaling dependent on the morphological factors of cells. The responsible molecules will be the "interface" between the membrane and the cytoskeleton, and may be indispensable to the special "shape" of each type of cells. Currently, we are focusing on the proteins that connect the membrane and cytoskeleton. These proteins include FBP17, Toca-1, syndapin, and IRSp53.

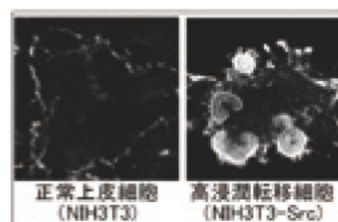

Fig.1 Podosomes formed by the activation of tyrosine kinase Src. The figures show the tyrosine phosphorylation of NIH3T3 cells (left) and NIH3T3 cells transformed with constitutive active mutant of Src (NIH3T3-Src cells).

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 studied so well. 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. Clarifying the nano-scale localization of these molecules will provide novel insights into the spatial organizations of these signaling 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.

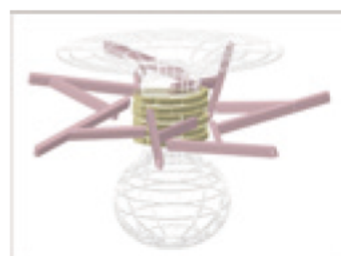

Fig.2 Wire-frame model of the clathrin-coated pit. The BAR proteins are shown in yellow, and the actin cytoskeleton is shown in magenta. The membrane is in wire-frame. The actin filaments are thought to be finely organized on the nano-scale membrane invaginations of the clathrin coated pits.

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Laboratory Microbial Molecular Genetics

▶ URL: http://bsw3.naist.jp/eng/courses/courses301.html

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Outline of Research and Education

At our laboratory, we have been studying how genetic information is precisely transmitted from parent cells to daughter cells and, conversely, how mutation is induced by inaccurate transmission of genetic information. To approach these questions, it is important to understand molecular mechanisms of genomic stability and molecular functions of DNA replication machineries. We are also exercising our best efforts in the international education of young students who are highly interested in basic issues related to DNA transaction (3R: Replication, Repair and Recombination) and the molecular mechanisms of biological evolution. We want to help our laboratory members become globally active individuals who act and think independently.

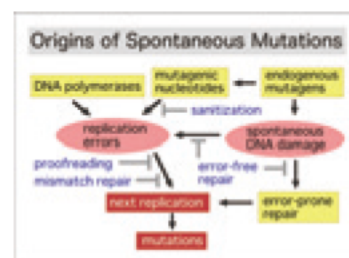

Fig.1 Multiple mechanisms suppress mutations. However, spontaneous DNA lesions serve as major causes of mutation under normal growth conditions.

Major Research Topics

1. Mechanisms for spontaneous mutation and its suppression (Fig.1)

- Onset of DNA replication errors and their repair (References 1 & 4)
- Generation of DNA damage due to oxygen radicals and its repair (References 1 & 3)
- Spontaneous mutation induced by cellular growth environments

2. Molecular mechanisms for genetic stability (Fig.2)

- Control mechanisms for genetic recombination
- Roles of DNA damage response and cell cycle checkpoint control (Reference 7)

3. Molecular functions of DNA replication machineries (Fig.3)

- Biochemical activities of DNA polymerases (References 2, 5 & 8)
- Replication fork arrest and its recovery processes (Reference 10)
- Dynamics of replication fork movement on genome (References 6 & 9)

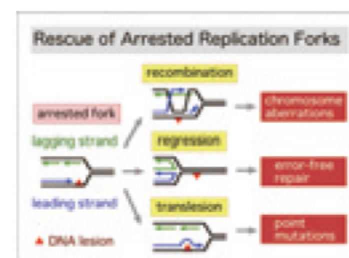

Fig.2 When DNA replication occurs without repair of DNA lesions, replication fork progression is inhibited. Mechanisms to rescue arrested replication forks include recombination repair, regression of replication forks and translesion DNA synthesis.

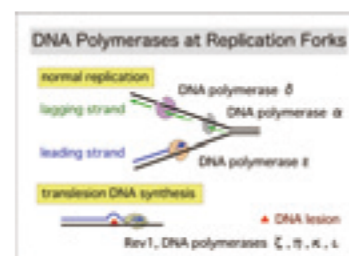

Fig.3 Multiple DNA polymerases ordinary work together for efficient DNA replication, thereby replication errors are suppressed. Special DNA polymerases work in both eukaryote and bacteria for translesion DNA synthesis.

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Laboratory Systems Microbiology

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Outline of Research and Education

Escherichia coli is undoubtedly one of the most studied organisms in the world. A vast amount of accumulated biological knowledge and methodologies makes this organism one of the ideal platforms to analyze cells at a systems level. Our lab is one of the leading groups performing post-genomic, systems and synthetic analyses using *E. coli* as a model system.

1. Genetic interactions

Normally cell systems can tolerate many kinds of perturbation, e.g. environmental changes and genetic mutations. In *E. coli,* most single gene knockout strains do not exhibit substantial phenotypic changes. This charactaristic is called "robustness" and is caused by the function of a network of compensatory backup systems. This is one of the main reasons why the computational design of a cell system has been unsuccessful so far. Genetic interaction analysis is one of the most reliable ways to identify and characterize cellular pathways. To determine the cellular network system in *E. coli,* we are performing high-throughput systematic genetic interaction studies using double-gene knockout strains.

2. Bar-code analysis

If each single gene knockout strain has a specific tag, and if we have a way to distinguish their tags from a single cell, then mixed cultures of all the deletion strains can be analyzed simultaneously to monitor population dynamics under competitive growth conditions. For this purpose, we developed a new single gene knockout mutant library carrying 20nt DNA sequences as a bar-code. To validate our approach, we are currently analyzing population changes during growth in a liquid medium for up to three weeks by monitoring the bar-code frequency of each of the deletion strains using deep sequencing methods.

3. Genome size design and cross-species transfer of DNA by conjugation

We have developed a very efficient method to construct double knockout strains using F-plasmid-based DNA-conjugation. The F- (*incF*) plasmid has a narrow host-range but *incP* and *incW* plasmid families have much wider host-ranges. We are expanding our conjugation vector system from the F-plasmid to the *incP* and *incW* plasmids to enable the transfer of large DNA molecules from E. coli into other microbes. Our long-term purpose is to design genome-size DNA molecules within constructed vectors and establish transfer systems to conjugate them into target micro-organisms.

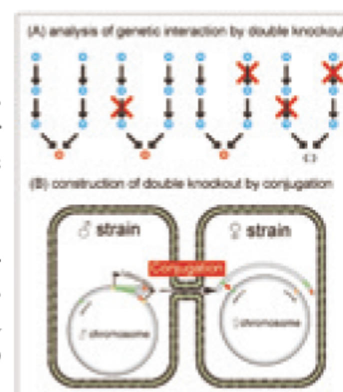

Fig.1 (A) The concept of synthetic lethal/sickness analysis: Red circles represent essential metabolites for cells. If cells have redundant routes to produce essential metabolites, double deletion methods may identify such redundant steps of genes (enzymes). (B) The conjugation method to generate double knockout strains by combining single knockout strains

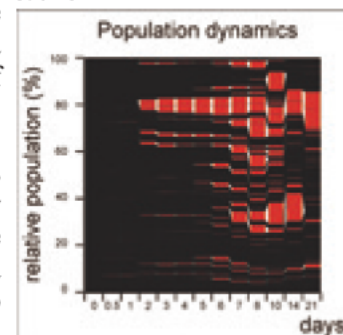

Fig.2 The X axis shows time points of samplings and the Y axis represents population ratio of all deletion strains.

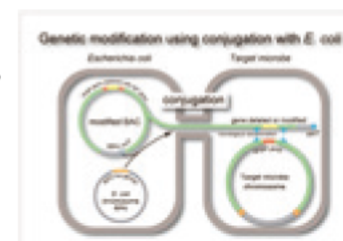

Fig.3 Wide host-range incP family plasmid RP4 can deliver large plasmid DNA by cross-species conjugation.

Major Research Topics

1. Genetic interaction networks

2. Quantitative metabolic network analysis

3. Development of artificial chromosome and cross-species transfer systems of huge DNA

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Laboratory 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* (Fig.1), which has been successfully used as a genetically amenable model system to investigate cellular regulatory mechanisms conserved from yeast to human. 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.

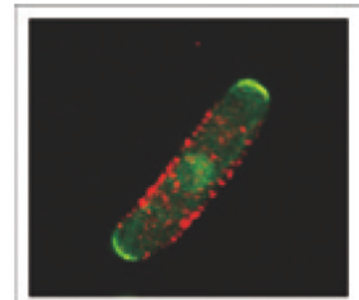

Fig.1 Fission yeast *Schizosaccharomyces pombe*

Major Research Topics

1. TOR (Target Of Rapamycin) signaling pathway

TOR kinase forms a protein complex called TORC2, which mediates insulin -induced activation of Akt kinase and cellular uptake of glucose (Fig.2). Defects in insulin signaling result in type 2 diabetes and therefore, comprehensive understanding of this pathway is crucial for the development of informed strategies to treat the disease.

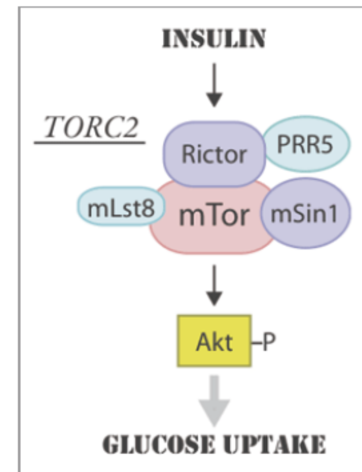

Fig.2 TOR complex 2 (TORC2) mediates insulin signals that induce cellular uptake of glucose.

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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Laboratory Applied Stress Microbiology

▶ URL: http://bsw3.naist.jp/eng/courses/courses305.html

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Outline of Research and Education

Our research involves "Applied Molecular Microbiology". The aims of our laboratory are basic studies in microbial science, particularly cellular response and adaptation to environmental stresses, and practical applications in new biotechnology. To fully understand microbial cell functions under stress conditions, we analyze and improve various mechanisms of microorganisms from molecular, metabolic and cellular aspects. As the best scenario, novel findings of our basic studies can be applied to the molecular breeding of useful microorganisms (yeasts, bacteria), the production of valuable biomaterials (enzymes, amino acids) and the development of promising technologies to solve environmental issues (bioethanol etc.).

Fig.1 Novel oxidative stress-tolerant mechanism in *S. cerevisiae*

Major Research Topics

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

We are interested in cellular response and adaptation to environmental stresses in the yeast *Saccharomyces cerevisiae*, which is an important microorganism in basic science 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 of yeast listed below.

- Proline: Metabolic regulation, transport mechanism, physiological functions
- *N*-Acetyltransferase Mpr1: Antioxidative mechanism, structural and functional analysis
- Nitric oxide (NO): Its synthetic mechanism and physiological roles
- Ubiquitin system: Quality control of abnormal proteins, regulation of the ubiquitin ligase Rsp5 activity

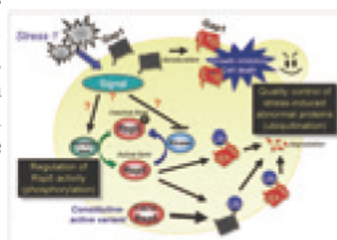

Fig.2 Ubiquitin system in *S. cerevisiae* under stress conditions

2. Physiological roles and metabolic regulation of cysteine in *Escherichia coli* (Fig.3)

L-Cysteine is an important amino acid both biologically and commercially. For achieving cysteine fermentation directly from glucose, we analyze the regulatory mechanisms of its biosynthesis, degradation and transport, based on genomic information and metabolic engineering. Also, we are interested in physiological roles of cysteine and its transporters in terms of redox regulation, and recently proposed that the inducible cysteine/cystine shuttle system plays a pivotal role in oxidative stress tolerance through providing a reducing equivalent to the periplasm in *E. coli*.

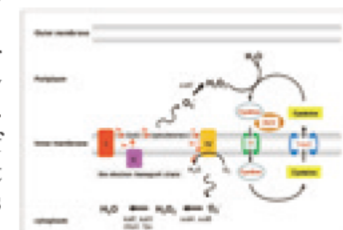

Fig.3 The cysteine/cystine shuttle system in *E. coli*

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1. Stress response and tolerance in yeast *Saccharomyces cerevisiae*

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2. Physiological roles and metabolic regulation of cysteine in *Escherichia coli*

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Laboratory Structural Biology

▶ URL: http://bsw3.naist.jp/eng/courses/courses306.html

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Outline of Research and Education

Proteins are folded into specific three dimensional (3D) structures, which are essential for imparting functions such as molecular recognition and catalysis. Without precise knowledge of their 3D-structures, we are unable to understand how proteins execute their respective molecular functions or rationally design inhibitors or drugs. Thus, the experimental determination of protein 3D-structures represents the hallmark of structural biology. Structural biology in our laboratory is performed using X-ray crystallography to determine the 3D-structures of proteins and molecular complexes at atomic resolution, and biochemical/biophysical analyses are performed to delineate the mechanisms by which proteins function at the atomic, molecular, and cellular levels.

Our general goal is to contribute towards our understanding of the nature of life. Our long-term objective is to understand the molecular functions of proteins and other biological macromolecules and their complexes in terms of molecular structures. Our efforts are directed towards defining the manner by which protein interactions and 3D-structures determine specificity and how structural changes enable functional switches in living cells.

We are expecting our lab to be an international one and welcome foreign students to study protein structures and functions.

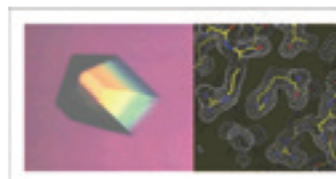

Fig.1 A crystal of histidine protein phosphatase (left), crystallized in our laboratory and part of its electron density map at 1.9 Å resolution obtained from X-ray crystal structure analysis

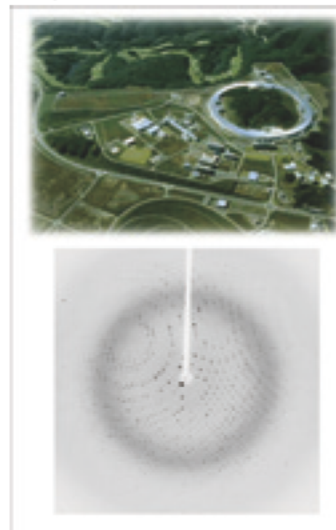

Fig.2 The SPring-8 synchrotron radiation facilities at Harima, Hyogo. We perform X-ray intensity data collection at SPring-8 for structure determination.

Major Research Topics

1. Structural molecular medicine

Drug-target proteins and other proteins important in medicine such as cancer, teratogenesis and infectious diseases

2. Structural cell biology

G proteins, their regulators and effectors, which play central roles in intracellular signal transduction regulating cell motility, adhesion and morphogenesis

3. Structural molecular biology

DNA recognition in DNA repair and transcription

4. Structural plant biology

Proteins that play pivotal roles in plant hormone signaling, such as receptors and master regulators

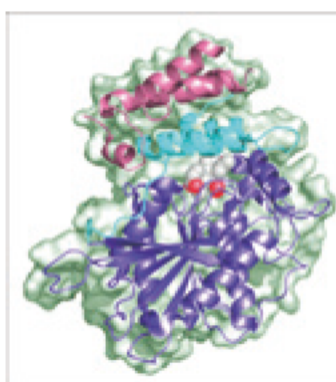

Fig.3 The ternary complex of gibberellin (space-filled model in white and red)-bound receptor GID1 (blue and cyan) trapping its downstream effector protein DELLA protein (pink) from our recent Nature article [4]

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Laboratory Membrane Molecular Biology

▶ URL: http://bsw3.naist.jp/eng/courses/courses309.html

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Outline of Research and Education

In the cell, a variety of membrane protein complexes is involved in the fundamental biological processes. The Sec membrane protein complex embedded in the cytoplasmic membrane in bacteria or the endoplasmic reticulum membrane in eukaryotes is the essential machinery for translocation of newly synthesized proteins across membranes (Fig.1). In bacteria, protein transport to the periplasm via a hetero trimeric complex called Sec translocon, composed of SecY, SecE and SecG, is driven by ATP-dependent motor SecA and proton-dependent motor SecDF cooperatively (Fig.2). We have determined crystal structures of all of the Sec factors [1,3,5,7] and performed structure-directed functional studies, which enabled us to propose conformational changes of Sec proteins during protein translocation. However, the details of the molecular mechanism remain unclear. Sec structures of other forms and at high resolution are required to fully understand Sec protein translocation machinery. In our laboratory, we perform structural biological analysis, including a new technique for visualizing the protein translocation (Fig. 3). Our results will lead to the understanding of not only protein transport across the membrane but also the transport mechanism of various materials including drugs.

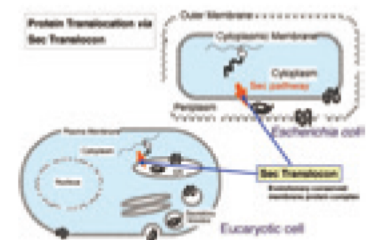

Fig.1 Conserved protein translocation across the membrane

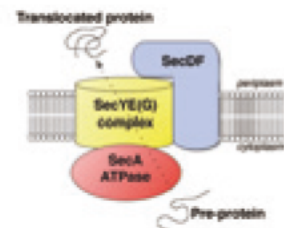

Fig.2 Bacterial Sec machinery: SecYEG complex provides the pore for protein movement that is driven by two motors, SecA and SecDF.

Major Research Topics

1. Protein transport across cell membranes

2. Molecular function and dynamics of membrane proteins

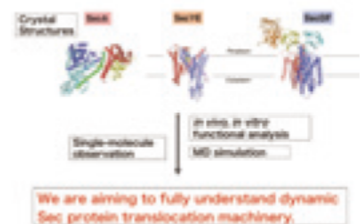

Fig.3 Our strategy for visualizing protein translocation

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Laboratory Gene Regulation Research

▶ URL: http://bsw3.naist.jp/eng/courses/courses308.html

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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.

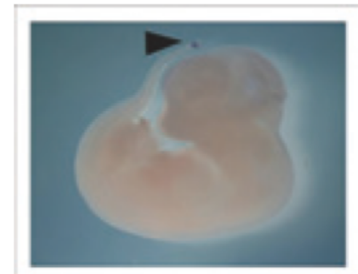

Fig.1 Transcription factor Hes7, serving as a molecular clock, is specifically expressed in the primordium of somites.

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 the 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.

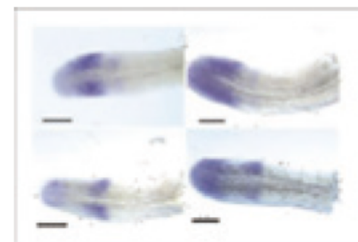

Fig.2 The expression of Hes7 oscillates in the primordium of somites.

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 (Fig.2, Fig.3). We are conducting studies to understand the biological clock in a comprehensive manner.

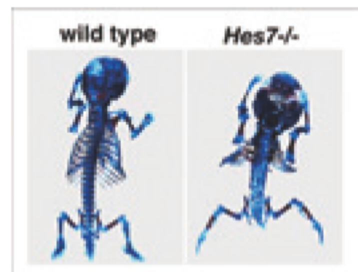

Fig.3 In Hes7 knockout mice, somite segmentation does not occur cyclically and the metameric structures along the anteroposterior axis are lost.

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Laboratory Systems Neurobiology and Medicine

▶ URL: http://bsw3.naist.jp/eng/courses/courses204.html

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Outline of Research and Education

During morphogenesis, biological systems self-organize their simple shapes into more complicated and beautiful ones. The goal of our studies is to understand deeply such a miraculous phenomenon, cellular morphogenesis. There are fundamental questions to be answered. Symmetry breaking (change of a symmetric shape to an asymmetric one) is an essential process of morphogenesis: theoretical models suggest that feedback loop and lateral inhibition may be involved, but how do the cellular molecules indeed give rise to these processes? Generation of mechanical forces is required to create cellular shape, but how? How do cells sense cellular length and size in order to regulate their size and morphology? Transport and diffusion of intracellular molecules would create unhomogeneous distribution: Do they play a role in cellular pattern formation? Is stochasticity utilized in cellular morphogenesis? All these questions are fascinating to us.

To untangle these issues, our laboratory focuses on neuronal morphogenesis and the proteins Shootin1, Shootin2 and Singar1, which we identified via proteome analyses. We analyze the molecular mechanisms for neuronal polarization, axon/dendrite formation and cell migration, using up-to-date methods including systems biology. We expect that these analyses will give us a new window into therapeutic strategies for neuronal diseases, such as nerve injury.

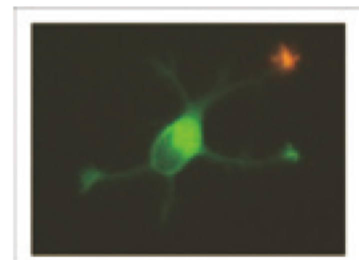

Fig.1 Shootin1 is a key molecule involved in neuronal symmetry breaking

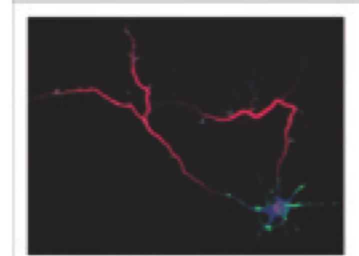

Fig.2 Singar knockdown leads to formation of surplus axons

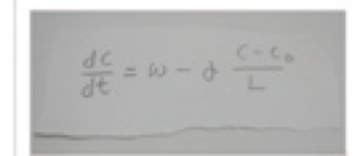

Fig.3 An equation to describe neurite length sensing by shootin1

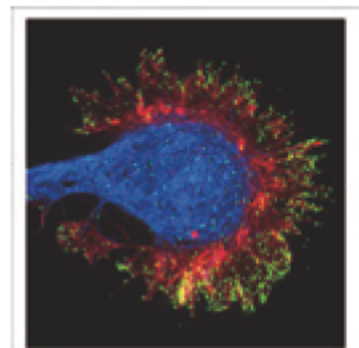

Fig.4 Signal-force transduction through shootin phosphorylation at growth cones

Major Research Topics

1. Axon/dendrite formation, neuronal polarization and migration
2. Generation of mechanical forces for neurite outgrowth and migration
3. Sensing of cellular length and size
4. Symmetry breaking
5. Tissue morphogenesis by molecular clutch

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Laboratory Plant Function Analysis

▶ URL: http://bsw3.naist.jp/eng/courses/courses901.html

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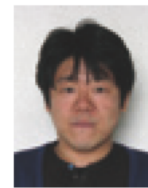
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Outline of Research and Education

Our laboratory started in 2010 within the framework of the Plant Science Global Top Education Program, supported by Japan's Ministry of Education, Culture, Sports, Science and Technology. The aims of this program are to establish an educational system linking nationwide universities and institutes, and to cultivate young plant researchers for the promotion of future plant science in Japan.

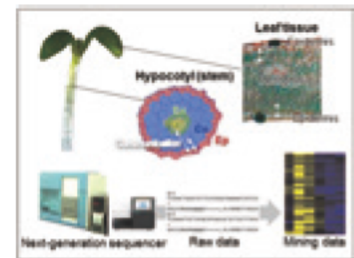

Fig.1 Coordinated growth among cell layers in Arabidopsis hypocotyl, and data from NGS

With the goal of promoting education on frontier technologies, we focus on rapidly advancing research fields such as genome-transcriptome analysis, biochemical and proteomic analysis of intracellular protein complexes, and visualization of those protein-protein interactions in living cells. Four researchers are assigned to this education purpose: Dr. Tetsuya Kurata has expertise in genome-transcriptome analysis with high-throughput next generation sequencer; Dr. Masayuki Fujiwara is a biochemist whose focus is on protein purification by various biochemical methods; Dr. Yoichiro Fukao specializes in proteomic analysis using the latest mass spectrometers; Dr. Noriko Inada is an expert of bioimaging using confocal and multiphoton microscopies.

Fig.2 LTQ-Orbitrap XL and TSQ-Vantage

Every year, we select up to 30 graduate students who have applied with their own research proposals employing genome-transcriptome analysis, biochemical and proteomic analysis, or bioimaging analysis to investigate plant protein function. These selected graduate students will benefit from one week of training in the above-mentioned cutting-edge technologies as well as avid interaction with other participating graduate students from various universities and institutes.

Major Research Topics

1. Genome-Transcriptome analysis (Tetsuya Kurata)
2. Purification and Analysis of Protein complex (Masayuki Fujiwara)
3. Proteome analysis (Yoichiro Fukao)
4. Bioimaging analysis (Noriko Inada)

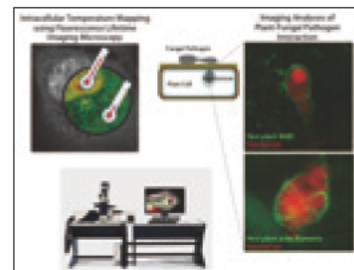
Fig.3 Imaging cellular temperature and powdery mildew-Arabidopsis interaction

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Laboratory NC-CARP (NAIST)

▶ URL: http://bsw3.naist.jp/eng/courses/courses902.html

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Outline of Research and Education

Network of Centers of Carbon Dioxide Resource Studies in Plants: NC-CARP is a project accepted by the plant science department of Green Network of Excellence (GRENE) which is sponsored by Japan's Ministry of Education, Culture, Sports, Science and Technology. NC-CARP has 11 institutions including NAIST and aspires to build a technological basis to turn carbon dioxide into resources. NC-CARP not only performs research, but also carries out its mission to educate the next generation of researchers who will take on the research of Carbon Dioxide Resources (Fig. 1) (http://nc-carp.org/index).

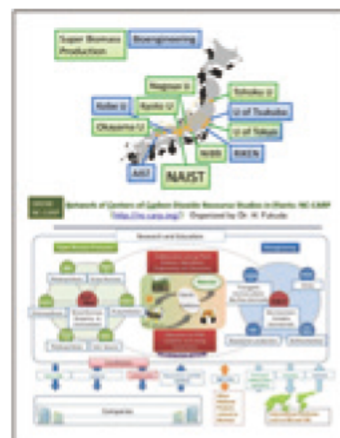

Fig.1 Summary of NC-CARP project NC-CARP forms a network of highly competent institutions in basic plant science studies, applied microorganism studies and bioprocessing technology.

Major Research Topics

1. Promotion of CO_2-storing Activity by Improving the Calvin Cycle (Enhancement of source) (Yohtaro Saito)

Improvement of photosynthetic efficiency in source leaves by strengthening the Calvin cycle enzyme activities increase biomass production. We have previously succeeded in increasing both photosynthetic activity and biomass production in tobacco and lettuce [6, 7]. We are trying the same approach in poplar.

2. Improvement of Tree Growth by Controlling Cell Proliferation (Enhancement of Sink) (Hidekazu Iwakawa)

To improve plant growth and yield, we aim to increase the ability of sink organs by enhancing cell proliferation. Previously we showed that, in Arabidopsis, a reduction in very-long-chain fatty acid (VLCFA) synthesis increased the cytokinin level, resulting in enhancement of cell division [2]. By using this strategy, we are developing technologies to inhibit VLCFA synthesis and increase woody biomass in poplar.

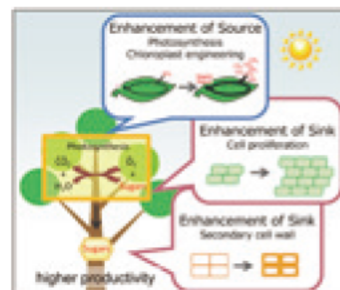

Fig.2 Research target of NAIST Enhancement of source and sink function in poplar.

3. Improvement of Woody Biomass Production by Enhancement of Cell Wall Formation (Enhancement of Sink) (Yoshimi Nakano)

The major component of woody biomass is the thickened cell wall (called "secondary cell wall (SCW)") of woody cells. We are aiming to enhance SCW formation to increase biomass production in GM poplar by introducing the key genes regulating SCW formation. Moreover, we will combine promotion of translocation and utilization of transport sugars to enhance woody biomass. [1, 3, 4, 5]

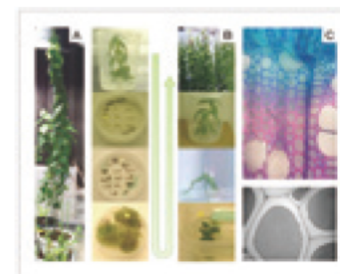

Fig.3 (A)Poplar, (B)Transformation and redifferentiation, (C)Microscopic observation.

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Outline of Research and Education

It is important to describe patient status accurately for proper diagnosis. One of the diagnostic methods for cancer is biomarkers, biological substances which accurately surrogate pathological parameter(s) of a patient. Exploration of new biomarkers is one of the major topics of current cancer research. Our main interest is the invention of new biomarkers based on nucleic acids.

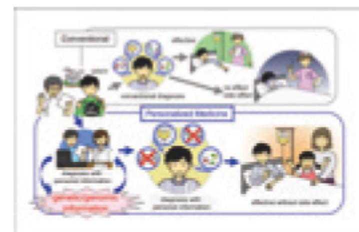

Fig.1 Personalized medicine

Major Research Topics

1. Noninvasive personalized medicine

Gefitinib is a good example of "personalized medicine"(Fig.1). It is only used for lung cancer with activating EGFR mutations. An important concern in clinical practice is that biopsy to obtain tumor samples is often difficult. In particular, biopsy for advanced or resistant cases is very difficult, and repeated sampling is almost impossible. A non-invasive technique such as detection of tumor DNA in peripheral blood is desirable.

We introduced a technique called BEAMing (beads, emulsion, amplification, matnetics) (Dressman et al., PNAS, 100, 8817, 2003), and used it for detection of EGFR mutations in plasma of lung cancer patients (Taniguchi et al., 2011). BEAMing and next-generation sequencers are based on the same technological principle. The mutations are sought with massively repeated sequencing of the EGFR gene fragments. We have already set up an assay system with a semiconductor sequencer (Fig.2), and are confirming its feasibility for EGFR mutation detection with Department of Thoracic Oncology.

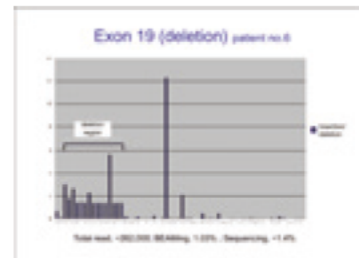

Fig.2 Detection of activating EGFR mutation in plasma of a lung cancer patient with massively repeated sequencing

2. Development of diagnosis and treatment methods via gene expression profiles

Gene expression profiling is one genomic approach, measuring expression levels of a large number of genes simultaneously. DNA chips and DNA microarrays are the most popular techniques. Instead, we developed a high-throughput quantitative PCR technique called adaptor-tagged competitive PCR (ATAC-PCR) (Kato, 1997), and have conducted analysis of more than 1,500 solid tumor tissues. The expression data and accompanying clinical information are stored in Cancer Gene Expression Database (CGED, http://lifesciencedb.jp/cged). The major outcomes include prediction of prognosis and docetaxel response in breast cancer, and prediction of prognosis in glioma (Shirahata et al. 2009) (Fig.3). In particular, we are confirming the performance of the glioma diagnostic system with samples in the Kitano Hospital, the National Cancer Center Hospital and Tokyo Women's Medical University Hospital.

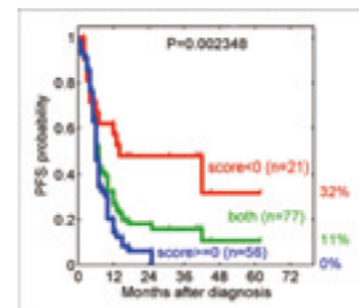

Fig.3 Kaplan-Meier analysis of glioma patients stratified with our prognosis predictor: All patients were stage IV.

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Outline of Research and Education

The development of multicellular organisms involves the collective effects of multiple events at the level of the individual cell, such as proliferation, differentiation, adhesion, and migration. Programmed cell death, for example, is a process by which cells are selected for death at set times in development, allowing for the sculpting of tissue, and is used in the adult organism to maintain homeostasis by eliminating cells that have developed abnormalities. Perturbations in cell death signaling can thus affect an organism's physiological stability, and result in developmental defects, tumorigenesis, or neurodegenerative disease. Cell death plays an important role in maintaining the cellular society not only by eliminating unneeded cells at given sites and stages, but in other functions, such as regulating the proliferation and migration of neighboring cells, as well. Such cellular behaviors give rise to cell networks capable of organizing into tissues, the study of which requires an experimental approach to spatiotemporal information in living systems, such as can be obtained through the real-time live imaging of biological phenomena. Our research goal is to elucidate the physiological roles of cell death and the basic mechanisms for regulating organogenesis using molecular, genetic and bioimaging approaches.

Major Research Topics

We have chosen the fruit fly *Drosophila* melanogaster as our primary research model, seeking to take advantage of its utility in developmental studies and wealth of genetic data in studying the coordination of histogenesis through live imaging and genetic screens. To elucidate the role of cell death in histogenetic processes, we will analyze caspase mutant phenotypes in which the exterior male genitalia (terminalia) develops abnormally. In normal *Drosophila* development, the terminalia rotates 360 degrees as it forms, but in caspase mutants, this revolution is incomplete. Image analysis reveals that in wildtype, the speed of this rotation is variable, with distinct initiation, acceleration, deceleration, and termination stages; caspase inhibition results in loss of the acceleration phase, and failure in terminalia development. We will seek to identify how caspase function and cell death control acceleration of the rotation through searching for associated genes and live imaging analysis. It is further predicted that cell death alone cannot account for the rotation that maintains tissue area, suggesting other mechanisms are also at work. We conduct single-cell analyses to determine whether other behaviors such as proliferation or migration are also altered. Through the use of the extensive *Drosophila* genetics toolset and live imaging technologies, we hope to be able to address questions that have proven technically challenging in the past, and, by visualizing the activities of individual cells, develop a better understanding of how cellular network systems work in histogenesis.

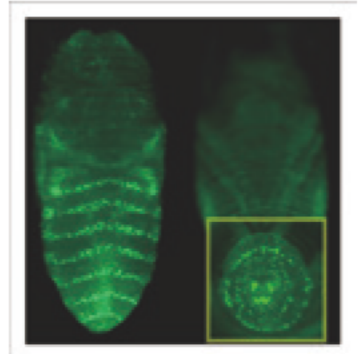

Fig.1 Dorsal (left) and ventral (right) views of Drosophila pupae that express fluorescent protein in cells located in the posterior component of each segment. Location of male genitalia is shown in the yellow square.

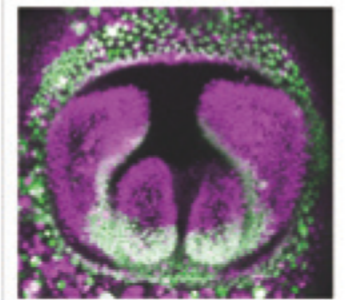

Fig.2 Caudal view of a Drosophila male terminalia showing cells in the posterior compartment (green).

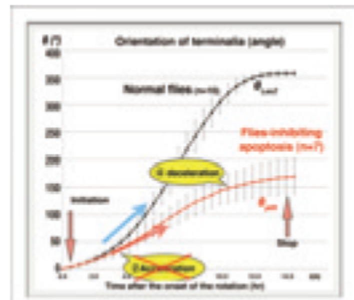

Fig.3 Comparison of the speed of genitalia rotation between normal flies and flies-inhibiting apoptosis.

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Affiliate Laboratory

Cell Growth Control

(with the Center for Developmental Biology, RIKEN)

▶ URL: http://bsw3.naist.jp/eng/courses/courses504.html

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Outline of Research and Education

The processes of animal development, including organ and body size, are genetically predetermined, but these processes are also influenced by environmental factors such as nutrition and temperature. The close link between cell and tissue growth control and environmental cues ensures that developmental transitions occur at the appropriate time during animal development. Our lab's research aims to shed light on the molecular basis for growth control and developmental timing at the cellular and tissue/organ level using the fruit fly Drosophila melanogaster and mammalian cell cultures as model systems. We combine biochemical and genetic approaches, along with quantitative and qualitative imaging and cell-biological analysis, to identify and characterize the relevant signal transduction pathways.

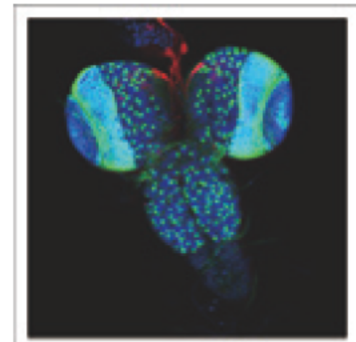

Fig.1 Larval central nervous system in Drosophila. Neural stem cells (green) and insulin-producing cells (red) are shown.

Major Research Topics

1. Molecular mechanisms of division arrest in neural stem cells

2. Molecular mechanisms of systemic growth and developmental timing

3. Molecular mechanisms of amino acid signaling

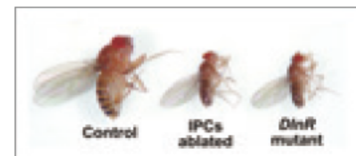

Fig.2 Drosophila mutants defective for systemic growth. Down regulation of the insulin signaling leads to the formation of small flies. The picture shows brain insulin-producing cell (IPCs) ablated flies and Drosophila insulin receptor (DInR) mutant flies.

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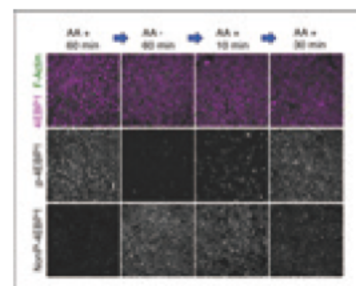

Fig.3 Amino acid response in cultured mammalian cell lines. The phosphorylation level of 4EBP1, a downstream target of the TOR kinase, is used as a readout of amino acid (AA) dependent activation of the TOR. Top panels indicate total 4EBP1 levels. Middle panels indicate phosphorylated 4EBP1, while lower panels indicate non-phosphoryated pools of 4EBP1.

Affiliate Laboratory

Molecular Microbiology and Genetics

(with Research Institute of Innovative Technology for the Earth (RITE))

▶ URL: http://bsw3.naist.jp/eng/courses/courses505.html

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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 required to solve these problems. Fundamental research employing microbial function 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

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). 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 a 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).

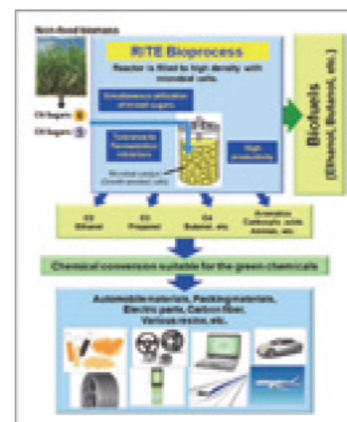

Fig.1 Biorefinery concept

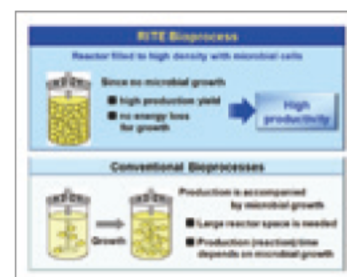

Fig.2 Novel features of the RITE Bioprocess

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.

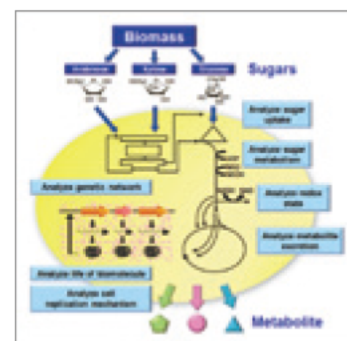

Fig.3 Breeding of recombinant strains using system biology

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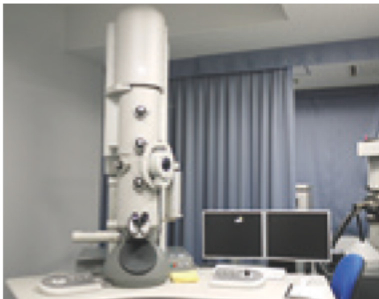
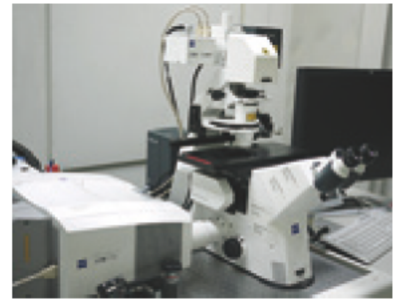
Abundant Research Facilities

Each department 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 School.



Transmission Electron Microscope

Scanning Electron Microscope

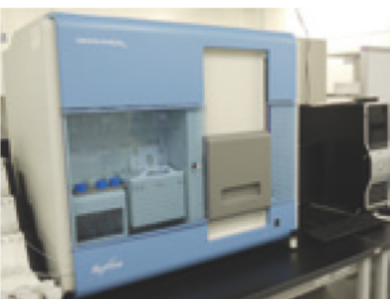


Confocal Laser Scanning Microscope

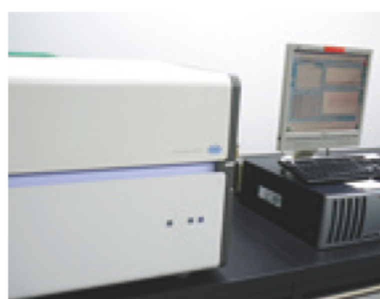
Spinning Disk Confocal Microscope

Flow Cytometry System

DNA Sequencer



Genome Analyzer IIx System



Real-Time PCR System

LTQ Orbitrap XL

TSQ Vantage

Protein Sequencer

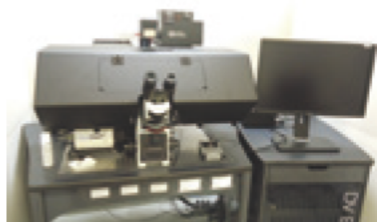
MALDI-TOF MS

GC-MS

In vivo Imaging System

Liquid Nitrogen Cryopreservation System

Ultra High-intensity Microfocus X-ray Generator・Macromolecular Crystallography Diffraction System


High Resolution Fluorescence Microscopy Imaging System