Nara Institute of Science and Technology NAIST®

Graduate School of
Biological Sciences

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NARA INSTITUTE of
SCIENCE and TECHNOLOGY

2017

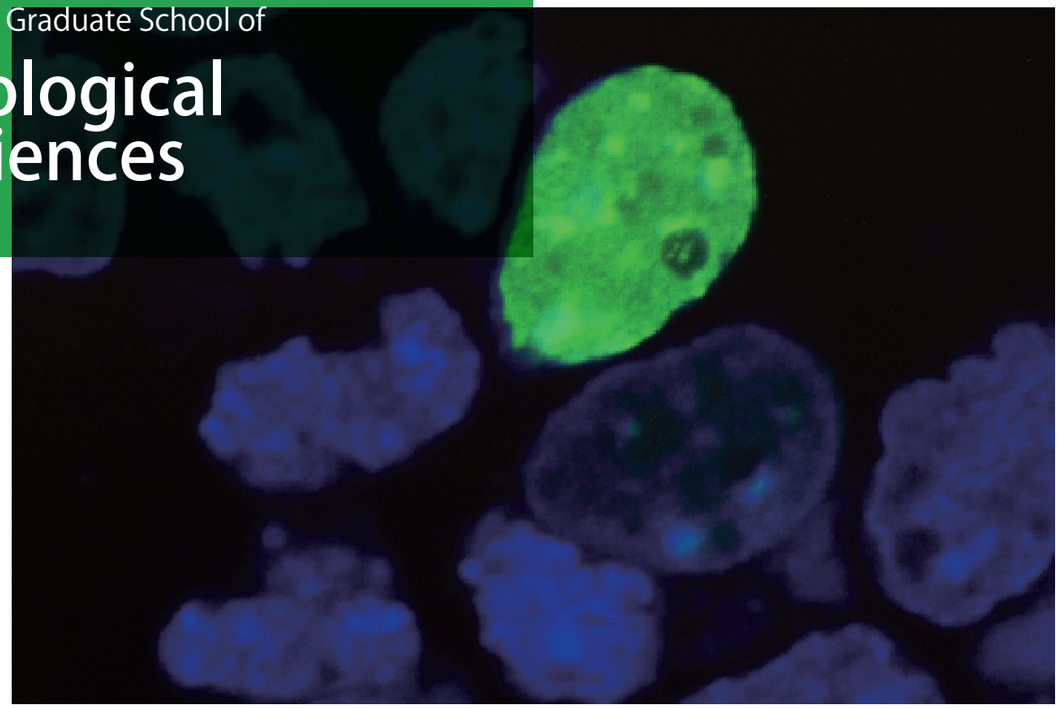
Graduate School of Biological Sciences

CONTENTS

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 mechanisms and pathways regulating living organisms, 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 Global COE programs, we elucidated the dynamic networks of molecules that comprise cells, using several advanced 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. Our programs for international students cultivate their abilities to play active roles in the international community of advanced life science and technology.

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, demonstrating our faculty and staff' s superior reputation both domestically and internationally.

Extensive research facilities

Each division is equipped with various state-of-the-art equipment. Additionally, the shared equipment provided at numerous locations within the School competes with the most advanced available facilities for biological science research in Japan.

Graduate school education with a comprehensive curriculum

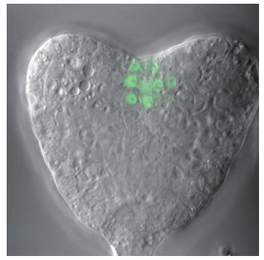
We provide two graduate courses to meet students' needs for their future careers: a two-year Bio-Expert course, and a five-year Frontier Bio course. We also offer an international course that provides a wide range of lectures covering the diverse fields of biological sciences in English.

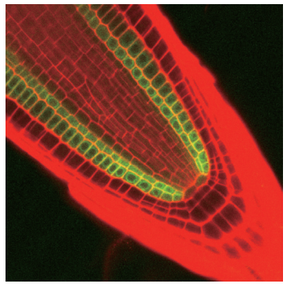
Support for student research and life

We have a strong support system for students, enabling them to focus on research without worrying about their daily life and expenditures. We offer scholarships from the Japan Student Services Organization and other public and private entities, and TA and RA funding for accomplished 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 produces various transgenic mice to support research. The Botanical Greenhouses comprise both open and closed green-houses. This facility houses various individual plants necessary for research activities, including transgenic plants.

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

Graduate School of Biological Sciences

Divisions & Faculty

(Based on April 1, 2017 data as of November, 2016)

Division of Plant Biology

Laboratory	Professor	Associate Professor	Assistant Professor
Plant Cell Function	Takashi Hashimoto	Tsubasa Shoji	Takehide Kato
Plant Developmental Signaling	Keiji Nakajima		Shunsuke Miyashima, Tatsuaki Goh
Plant Metabolic Regulation	Taku Demura	Ko Kato	Arata Yoneda, Misato Ohtani
Plant Growth Regulation	Masaaki Umeda		Naoki Takahashi, Hirotomo Takatsuka
Plant Stem Cell Regulation and Floral Patterning	Toshiro Ito		Nobutoshi Yamaguchi
Plant Immunity		Yusuke Saijo	Kei Hiruma, Yuri Tajima
Plant Symbiosis		Satoko Yoshida	

Division of Biomedical Science

Laboratory	Professor	Associate Professor	Assistant Professor
Molecular Signal Transduction	Hiroshi Itoh		Tetsuo Kobayashi, Noriko Kaji
Functional Genomics and Medicine		Yasumasa Ishida	Nanaho Fukuda
Tumor Cell Biology	Jun-ya Kato		Takashi Yokoyama
Molecular Immunobiology	Taro Kawai		Takumi Kawasaki, Daisuke Ori
Applied Immunology	Reiko Shinkura		Keiko Nakanishi
Molecular Medicine and Cell Biology	Shiro Suetsugu		Kyoko Hanawa
Developmental Biomedical Science		Noriaki Sasai	Akiko Nishi-Hori
Organ Developmental Engineering		Ayako Isotani	

Division of Systems Biology

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

Humanophilic Innovation Project

Laboratory	Professor	Associate Professor	Assistant Professor
Humanophilic Innovation Project	Taku Demura	Minoru Kubo	

Affiliate Laboratories

Laboratory	Professor	Associate Professor
Molecular Genetics of Human Diseases (with Osaka Medical Center for Cancer and Cardiovascular Diseases)		Yoji Kukita
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	

Graduate School of Biological Sciences

Graduate School of Biological Sciences

Areas of Research and Education

Division of Plant Biology

The mission of the Division of Plant Biology is to cultivate professionals with advanced knowledge and skills in basic and applied biology research to contribute to sustainable social development. Basic research topics are related to: plant development, cell cycle regulation, cell differentiation, organ formation, genetic regulation, reproduction, photosynthesis, information transfer, stress response, and environmental response. Applied research activities address environmental, resource, and food supply problems, such as the enhancement of plant productivity and environmental tolerance.

Key Laboratories

Plant Cell Function

Professor Takashi Hashimoto
Associate Professor Tsubasa Shoji
Assistant Professor Takehide Kato

The laboratory's research and educational activities target plant gene functions regulating cytoskeletal formation, cell shape determination, and secondary metabolism, using mutants, transgenics, cell and tissue cultures, and cell biological techniques.

- Microtubules, left-right asymmetry, environmental response, signal transduction, secondary metabolism, metabolic engineering to produce useful compounds, wound response

Plant Developmental Signaling

Professor Keiji Nakajima
Assistant Professor Shunsuke Miyashima
Assistant Professor Tatsuaki Goh

Research and educational activities are performed to explore the mechanisms of plant growth regulation at the cell differentiation and pluripotency control levels using molecular genetics and live imaging techniques.

- Plant growth control, cell differentiation, tissue formation, meristem, embryogenesis, reprogramming, germ cell specification, signal transduction, transcription factors, microRNA, epigenetics

Plant Metabolic Regulation

Professor Taku Demura
Associate Professor Ko Kato
Assistant Professor Arata Yoneda
Assistant Professor Misato Ohtani

Our research and educational efforts aim at studying the mechanisms for plant cell differentiation and functional and metabolic regulation of plant cells, to develop novel biotechnological tools leading to the establishment of a sustainable society.

- Wood biomass, cell differentiation, cell walls, genetic regulation, wood biotechnology, molecular breeding, plant-based production of useful compounds

Plant Growth Regulation

Professor Masaaki Umeda
Assistant Professor Naoki Takahashi
Assistant Professor Hirotomo Takatsuka

Laboratory research and educational activities are centered on DNA polyploidization, DNA damage response, and organ size control in plants. Regulatory mechanisms underlying cell division and cell growth are investigated to develop technologies for increasing plant biomass.

- Plant biomass, endoreplication, cell cycles, DNA damage, plant hormones, chromatin structure, stem cells, cell division, cell growth, signal transduction

Plant Stem Cell Regulation and Floral Patterning

Professor Toshiro Ito
Assistant Professor Nobutoshi Yamaguchi

For research and education, we concentrate on the genetic mechanisms for spatiotemporal specific regulation, developmental coordination of multiple genes, and environmental response in flower development, focusing on epigenetic changes and their upstream signaling pathways.

- Flower development, molecular genetics, genomics, synthetic biology, chromatin, epigenetics, signal transduction, homeotic transcription factors, meristem, environmental response

Plant Immunity

Associate Professor Yusuke Saijo
Assistant Professor Kei Hiruma
Assistant Professor Yuri Tajima

Research and education activities focus on the dynamic and reciprocal interactions between plants and pathogenic and symbiotic microorganisms to elucidate plant immune regulation and microbial infection strategies on the molecular level.

- Plant immunity, danger sensing and signaling, receptors, signal transduction, coordination between biotic and abiotic stress responses, regulation and epigenetic memory of gene expression, endophytes, genomics, infection strategy, microbial effectors, coevolution

Plant Symbiosis

Associate Professor Satoko Yoshida

Laboratory research and education programs address the interaction between plants and other organisms, especially parasitic and host plant interaction, using molecular genetics and genomics.

- Parasitic plants, Striga, root architecture, weed science, plant-plant interaction, genomics, bioinformatics, evolution, chemical communication, molecular biology, molecular genetics

Division of Biomedical Science

The mission of the Division of Biomedical Science is to equip students with advanced biomedical knowledge and skills in basic and applied research to contribute to a healthier society. Basic research activities are related to cellular, tissue, organ, and systemic mechanisms of life, such as growth and development, cell proliferation control, cell differentiation, organ formation, genetic regulation, information transfer, homeostasis, and stress response. Applied research areas include neurological, metabolic, malignant, and other chronic diseases, with a focus on elucidating their etiology and pathogenesis.

Key Laboratories

Molecular Signal Transduction

Professor Hiroshi Itoh
Assistant Professor Tetsuo Kobayashi
Assistant Professor Noriko Kaji

Research and education efforts are geared toward elucidating the mechanisms of human development and homeostasis by analyzing cell response to hormones, neurotransmitters, and other molecules involved in cell differentiation and proliferation. Efforts are also geared toward the diagnosis and treatment of cancer, neurological disorders, lifestyle diseases, and other chronic conditions.

- Signal transduction mechanism, G-protein, tumor cell adhesion and migration, molecularly targeted drugs, functional antibodies, new receptor-binding ligand, growth, differentiation, and migration of neural stem cell, formation and function of primary cilia

Functional Genomics and Medicine

Associate Professor Yasumasa Ishida
Assistant Professor Nanaho Fukuda

We try to elucidate the yet to be discovered functions of PD-1 in the “self-nonself” discrimination of the immune system. We also investigate the molecular mechanisms involved in the localization of the odorant-receptor mRNAs in olfactory sensory neurons.

- PD-1, immunity, cancer, immunotherapy, olfactory sensory neurons, mRNA localization, nonsense-mediated mRNA decay, translation arrest, ES cells, gene traps, knockout mice

Tumor Cell Biology

Professor Jun-ya Kato
Assistant Professor Takashi Yokoyama

Our research and education activities address the molecular mechanisms regulating tumor cell growth, differentiation, and survival, with a particular interest in mammalian cell cycle control, senescence, differentiation, apoptosis, autophagy, and stem cell regulation.

- Cell cycle regulation, checkpoint control, cellular carcinogenesis, leukemia, hematopoietic stem cells, cancer stem cells, genetically modified mice, cell senescence, cell differentiation, apoptosis, p53, proteolytic regulation, constitutive photomorphogenesis 9 (COP9) signalosomes

Molecular Immunobiology

Professor Taro Kawai
Assistant Professor Takumi Kawasaki
Assistant Professor Daisuke Ori

Research and education activities revolve around immune response mechanisms, specifically including the pathogenesis of autoimmune disorders, allergies, inflammatory diseases, and other chronic conditions that occur as a result of aberrant immune response. New diagnostic and therapeutic methods for immunity-related illnesses are also explored.

- Innate immunity, signal transduction, cytokine, inflammation, autoimmune disease, allergies, vaccine development, knockout mice

Applied Immunology

Professor Reiko Shinkura
Assistant Professor Keiko Nakanishi

Our research focuses on the molecular mechanisms of antibody diversification accompanied by genetic alterations such as somatic hypermutation and class switch recombination. Our final goal is to apply newly achieved knowledge to antibody engineering and practical medicine.

- Antibodies, somatic hypermutation, class switch recombination, antibody engineering, mucosal immunity, acquired immunity, B cell activation, gut microbiota, genome instability, DNA repair

Molecular Medicine and Cell Biology

Professor Shiro Suetsugu
Assistant Professor Kyoko Hanawa

Laboratory research and education efforts aim to explore cell membrane morphogenesis and lipid-mediated signal transduction, particularly areas related to the molecular mechanisms of protein-lipid coupling and the cellular and organismal processes of morphogenesis and pathogenesis. Lipid metabolism is also considered.

- Lipid membranes, cytoskeletons, signal transduction, cell mobility, super-resolution analysis, imaging, crystallography, cancer, hereditary disease, systems biology

Developmental Biomedical Science

Associate Professor Noriaki Sasai
Assistant Professor Akiko Nishi-Hori

We are interested in how the diversity of cell types can be produced from a limited number of genes, focusing on vertebrate neural development as a model system.

- Neural development, neural tube, pattern formation, signal transduction, Sonic Hedgehog, chick, mouse, cilia, retinopathy, membrane protein

Organ Developmental Engineering

Associate Professor Ayako Isotani

We analyse organs, tissues and cells developed in xenogeneic chimera or by xenogeneic transplantation. Through these findings, we investigate the essential factors for correct function with the aim of performing a basic studies leading to regenerative medicine.

- Organ formation, developmental engineering, stem cells, transplantation, regenerative medicine, xenogeneic chimera, disease model animals

Graduate School of Biological Sciences

Areas of Research and Education

Division of Systems Biology

The mission of the Division of Systems Biology is to facilitate students' advance system-based research on biological processes, such as heredity, evolution, cell growth, environmental response, tissue and organ formation, development, and neural network formation. Research approaches include mathematical modeling methods and experimental methods in cell and molecular biology. This division is also dedicated to fostering professionals capable of introducing new, innovative methods and techniques, such as information and nano technology, into bioscience research.

Key Laboratories

Microbial Molecular Genetics

Professor Hisaji Maki
Associate Professor Masahiro Akiyama
Assistant Professor Asako Furukohri

Our research and education activities focus on i) the mechanisms supporting faithful transmission of genetic information and ii) the process of gene mutation and chromosomal rearrangement and aberration leading to alteration of genetic information.

- DNA replication, repair, and recombination, mutation, chromosomal rearrangement, evolution, cell growth, cell cycle control, oxygen radical–induced DNA damage, DNA damage response

Systems Microbiology

Professor Hirotada Mori
Assistant Professor Ai Muto

The laboratory's research and education activities revolve around the systems biology approach to fully understanding the cellular function network. Escherichia coli, one of the most extensively studied model organisms, is used for genome-wide interaction analysis to establish network biology.

- Network biology, systems biology, genome analysis, interactomes, transcriptomes, proteomes, metabolomes

Cell Signaling

Professor Kaz Shiozaki
Assistant Professor Hisashi Tatebe

Elucidation of the structure and function of the cellular signaling network conserved from yeast to humans, aiming to understand the molecular basis of cellular dysfunction in human diseases.

- Protein phosphorylation, protein interaction network, yeast molecular genetics, genome editing, cell imaging, diabetes, cancerous cell proliferation

Applied Stress Microbiology

Professor Hiroshi Takagi
Assistant Professor Daisuke Watanabe
Assistant Professor Ryo Nasuno

Research and education activities focus on the molecular mechanisms of cellular response and adaptation to environmental stresses using microorganisms, yeasts and bacteria. The lab also addresses their applications to biotechnology, such as the breeding of industrial yeast strains and the production of functional amino acids.

- Applied molecular microbiology, molecular breeding, biomass production, functional modification of yeast, genomic information, metabolic regulation, environmental stress response and tolerance, signal transduction, physiological functions of amino acid, redox regulation, control of protein activity, carbon dioxide fixation

Structural Biology

Professor Toshio Hakoshima
Assistant Professor Ken Kitano
Assistant Professor Tomoyuki Mori

Proteins play a key role in the complexity and flexibility of many biological processes. The lab is dedicated to three-dimensional atomic analyses of protein functions, such as substrate specificity and dynamic conformation-mediated regulation of activity and function.

- Structural cell biology, structural and molecular medicine, structural botany, chemical biology, protein crystallography, intracellular signal transduction, cell adhesion and cytoskeleton, mechanical sensor proteins, drug-targeted proteins, plant hormone receptors

Membrane Molecular Biology

Associate Professor Tomoya Tsukazaki
Assistant Professor Yoshiki Tanaka

Various membrane protein complexes are involved in fundamental biological events. Our education and basic research projects address the molecular framework for the dynamic changes in such complex molecules, using a combination of new structural biology methods.

- Protein science, structural bioscience, protein transport, three-dimensional protein structure, protein interaction, membrane protein complexes, translocon, molecular mechanisms, membrane transporters, crystallography

Gene Regulation Research

Professor Yasumasa Bessho
Associate Professor Takaaki Matsui
Assistant Professor Yasukazu Nakahata

Our research and education programs are focused on the study of the guiding principles for dynamic biological events, such as i) segmentation in vertebrate development, ii) circadian and other biological rhythms, and iii) cell motility and pattern formation in the developmental process.

- Vertebrate segmentation, gene expression control, temporal regulation of developmental processes, circadian clocks, cell mobility, left-right pattern formation, live imaging

Systems Neurobiology and Medicine

Professor Naoyuki Inagaki
Assistant Professor Akihiro Urasaki
Assistant Professor Michinori Toriyama

Research and education activities center around the morphogenesis of neuronal cells and tissue, with a particular focus on signal transduction, cytoskeletons, and intracellular transport. Comprehensive methodological approaches encompassing molecular, cellular, and developmental biology methods, force sensing, and mathematical models are applied. Additional scientific interests also include pathologies resulting from morphogenetic failure and development of therapeutic measures.

- Neural circuits, axons, polarity, symmetry breaking, cell mobility, cytoskeletons, intracellular molecular transport, traction force, signal transduction, live imaging, knockout mice, zebra fish, systems biology, regenerative medicine

Humanophilic Innovation Project

Humanophilic Innovation Project		Interdisciplinary research and educational activities integrating the fields of biological, material and information sciences aim to develop novel human life support systems.
Professor	Taku Demura	● QOL, genome breeding, green materials, organic super molecules, eco devices, micro photonic devices, imaging sensors, smart homes, context awareness
Associate Professor	Minoru Kubo	

Affiliated Laboratories

NAIST has established cooperative agreements with several scientific institutes in the Kinki region to promote top-notch bioscience research and education. Selected researchers from these institutes with proven academic and teaching excellence are invited as affiliate professors to supervise master's and doctoral programs. Bioscience students are given the opportunity to pursue their thesis or dissertation projects in one of these affiliated laboratories.

Laboratories

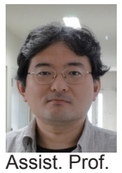
Molecular Genetics of Human Diseases		Research and education projects are aimed at developing new cancer diagnostic tools. For this purpose, genome-wide analysis and other molecular biology techniques are employed to analyse human lesion tissue.
Associate Professor	Yoji Kukita	● Molecular diagnosis of cancer, molecularly targeted drugs, cancer immunotherapy, transcriptomes, whole genome analysis (Affiliation: Osaka Medical Center for Cancer and Cardiovascular Diseases)
Cell Growth Control		Basic research and education projects address the molecular basis of cell and tissue signal transduction involved in the temporal regulation of development and growth.
Associate Professor	Takashi Nishimura	● Cell growth and proliferation, signal transduction, Drosophila, body size, developmental timing, metabolic control (Affiliation: Riken Center for Developmental Biology)
Molecular Microbiology and Genetics		Basic research and education activities focus on the development of a biorefinery, a facility that integrates biomass conversion and environment-friendly production of fuels and other useful chemicals. To achieve this, integrated omics analysis and metabolic conversion techniques are employed to develop new microbial functions.
Professor	Masayuki Inui	● Microbiology, molecular biology, genome engineering, culture engineering, metabolomic analysis, metabolic engineering, systems biology, high-efficiency bioprocess (Affiliation: Research Institute of Innovative Technology for the Earth (RITE))

Laboratory Plant Cell Function

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


Prof. Takashi Hashimoto


Assoc. Prof. Tsubasa Shoji


Assist. Prof. Takehide Kato

E-mail { hasimoto, t-shouji, t-kato }@bs.naist.jp

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 technology on Arabidopsis thaliana, tobacco, and tomato.

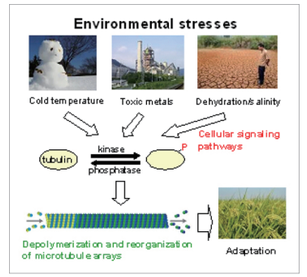


Fig. 1 Environmental stresses remodel the microtubule cytoskeleton by phosphorylation of tubulin subunits.

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

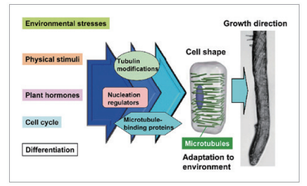


Fig. 2 The plant microtubule cytoskeleton remodels in response to developmental and environmental signals, and controls plant cell shape.

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

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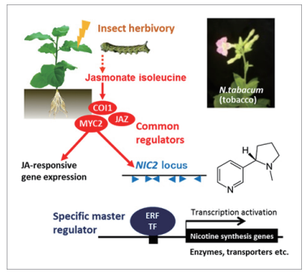
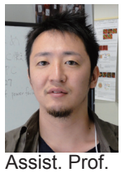


Fig. 3 Jasmonate-responsive ERF transcription factor genes clustered at NIC2 locus regulate nicotine biosynthesis in tobacco.

Laboratory Plant Developmental Signaling

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


Prof.
Keiji Nakajima


Assist. Prof.
Shunsuke Miyashima


Assist. Prof.
Tatsuaki Goh

E-mail { k-nakaji, s-miyash, goh }@bs.naist.jp

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 both intercellular and intracellular signal transduction pathways underlying the pattern formation and cell differentiation of roots and embryos, as well as cell reprogramming that triggers embryogenesis.

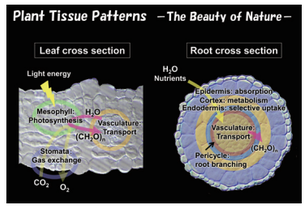


Fig. 1 (Left) In leaves, specialized cell types such as mesophyll, stomata, and vascular cells, are spatially arranged to maximize photosynthetic ability. (Right) Root tissues are organized into a concentric pattern that facilitates water and nutrient uptake, as well as their metabolism and translocation.

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 have revealed the presence of novel signaling pathways that allow regulatory molecules such as transcription factors and microRNAs to travel from cell to cell (Fig.2). We are currently focusing on the generality of such cell-cell signaling pathway in root and embryo patterning.

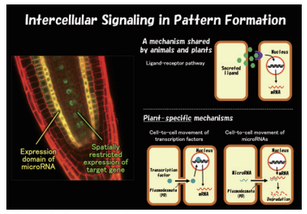


Fig. 2 Plant cells are connected with a cytoplasmic continuum termed plasmodesmata (PD). PD allows passage of regulatory molecules, such as transcription factors and small RNAs, thereby serving as a channel to transmit developmental signals.

2. Cell reprogramming and pattern formation during embryogenesis and germ cell formation

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- and germ cell-specific developmental program is initiated only after the reprogramming of somatic cells to the embryonic status. We have recently discovered a key reprogramming factor in Arabidopsis and bryophytes, and are currently investigating their 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.

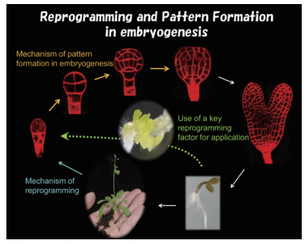


Fig. 3 Pattern formation in embryogenesis is triggered by cell reprogramming and proceeds in a highly ordered manner. We study the mechanisms underlying embryonic pattern formation and reprogramming, as well as application of the reprogramming factors for efficient propagation of useful plants.

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Laboratory Plant Metabolic Regulation

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


Prof.
Taku Demura


Assoc. Prof.
Ko Kato


Assist. Prof.
Arata Yoneda


Assist. Prof.
Misato Ohtani

E-mail { demura, kou, arata-yoneda, misato }@bs.naist.jp

Outline of Research and Education

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

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

Major Research Topics

1. Molecular mechanisms governing xylem cell differentiation

We identified a key regulator of the xylem vessel differentiation, Arabidopsis VND7 (Vascular-Related NAC Domain Protein7), which is a plant-specific NAC domain transcription factor (Fig.1). To understand the molecular mechanism by which xylem vessel formation is regulated, we have been characterizing VND7 and its homologs through various approaches (Fig. 2).

2. Molecular and cell biological approaches to improve woody biomass

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

3. Highly-efficient transgene expression systems of higher plants

In order to transcribe foreign genes in plant cells more effectively, we are studying the factors that contribute to transgene-silencing, the relationship between chromatin/nucleosome structure around the promoter region and gene expression, identification and characterization of matrix the attachment regions, and improvement of transcriptional terminator regions.

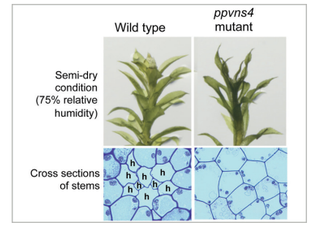

Fig. 2 Moss Physcomitrella patens ppvns mutants, a knock out mutant for one of VND-homologous genes, show the malformation of hydroids (h) in stems, thus leading to decreased water transport activity accompanied wilting phenotype under semi-dry conditions.

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Laboratory Plant Growth Regulation

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


Prof. Masaaki Umeda
Assist. Prof. Naoki Takahashi
Assist. Prof. Hirotomo Takatsuka
E-mail { mumeda, naoki, h-takatsuka }@bs.naist.jp

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 and cell growth in a precise, spatiotemporal manner to achieve proper development of organs under changing environmental conditions. However, little is known about how cell division and growth is regulated, and how plants maintain DNA integrity during organ growth and development. We focus on the molecular mechanisms underlying DNA polyploidization and DNA damage response, and also on organ size control. Our studies will uncover how internal and external factors, such as plant hormones and environmental stress, converge onto the machineries controlling cell division and growth, thus developing technologies to increase plant biomass.

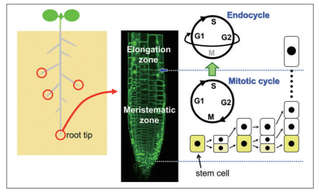

Fig. 1 Cell cycle regulation in root growth

Major Research Topics

1. DNA polyploidization (Fig.1, Fig.2)
- Control of the transition from cell division (mitotic cycle) to endoreplication (endocycle)
- Epigenetic regulation of competence in DNA polyploidization
- Development of technologies increasing biomass productivity in poplars

2. DNA damage response
- DNA damage checkpoints controlled by transcription factor SOG1
- Stem cell maintenance under DNA damage conditions
- Crosstalk between DNA damage response and defense response

3. Organ size control (Fig.3)
- Epidermis-derived signals controlling cell division in internal tissues
- Crosstalk between brassinosteroid signaling and cytokinin biosynthesis
- Control of cell-to-cell communication by very-long-chain fatty acids (VLCFAs)

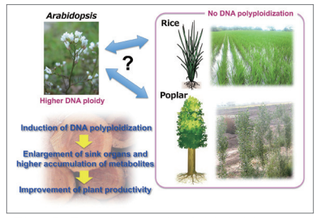

Fig. 2 Development of high-biomass plants by induction of DNA polyploidization

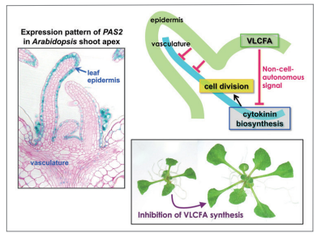

Fig. 3 Epidermis-derived signals control organ size. VLCFA, very-long-chain fatty acids; PAS2, PASTICCINO2

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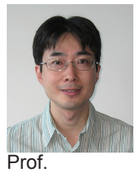
Laboratory Plant Stem Cell Regulation and Floral Patterning

▶ URL: http://bsw3.naist.jp/eng/courses/courses112.html




Prof. Toshiro Ito
Assist. Prof. Nobutoshi Yamaguchi
E-mail { itot, nobuy }@bs.naist.jp

Outline of Research and Education

We are interested in the **developmental coordination** of proliferation and differentiation, and **spatiotemporal-specific gene regulation** in flower development. We also explore **environmental response and acclimation**. To reveal these molecular mechanisms, we use *Arabidopsis* as a model plant for genetic, reverse-genetic, biochemical and genomics approaches, especially focusing on epigenetic histone modification. We also use rice to study its conservation and diversification. Our students work at the frontiers of plant molecular genetics, developing their research, presentation and writing skills.

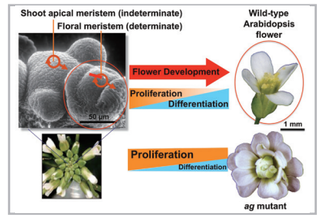


Fig. 1 *Arabidopsis* flower development
In flower development, the stem cell activities in the floral meristem are terminated (determinate), while the shoot apical meristem continues to grow.

Major Research Topics

1. Cell-cell signaling cascades controlling floral stem cell maintenance and cross-talk with transcriptional cascades

Flowers originate from self-renewing pluripotent stem cells in the floral meristems. The maintenance and differentiation of stem cells are regulated by a well-coordinated interplay of cell-cell signaling and transcriptional events. In flower development, the expression of the stem cell determinant *WUS* is terminated by multiple pathways. We study the cross-talk of multiple feedback pathways controlling *WUS* expression and reveal the molecular basis of developmental coordination (Fig. 1).

2. Transcriptional cascades controlling floral stem cell termination

Floral stem cell termination is regulated by a multi-step process mediated by at least four transcription factors (Fig. 2). AG's function in the meristem determinacy is mediated mainly by *KNU* and *CRC* as the direct targets. SUP regulates the meristem determinacy independent of AG. We study how KNU, CRC and SUP regulate floral stem cell activities and reveal the mechanisms of spatiotemporal-specific gene regulation.

3. Environmental response and acclimation

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

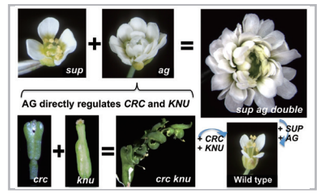


Fig. 2 Floral stem cell termination
The double mutant of *sup* and *ag* shows an enlarged flower with a fasciated meristem in the center. The *crc knu* double mutant has a shoot inside the carpels.

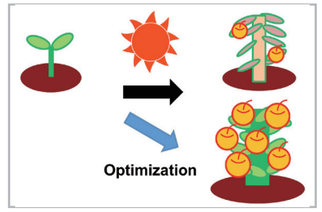


Fig. 3 Plant growth optimization
By revealing the mechanisms of floral stem cell regulation and environmental responses, we will develop a molecular basis for plant growth optimization for higher crop yield.

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Laboratory Plant Immunity

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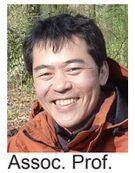
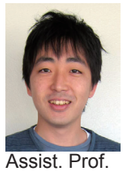

Assoc. Prof.
Yusuke Saijo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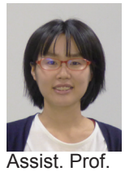
Kei Hiruma


Assist. Prof.
Yuri Tajima

E-mail { saijo, hiruma, ytajima }@bs.naist.jp

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 endophytic microbes at non-damaging levels, despite an elaborate innate immune system to detect and repel microbes. We hypothesize that plants distinguish pathogens from non-pathogens by sensing "danger" signals (DAMPs) generated upon pathogen challenge in addition to microbial signals (MAMPs). We aim to decipher the molecular principles and mechanisms underlying plant immunity to infectious microbes, with major focuses on signaling crosstalk between MAMP and DAMP receptors, defense-related transcriptional reprogramming and infection strategies of pathogenic and endophytic microbes. We also study the mechanisms by which a subset of endophytic microbes facilitates host adaptation to adverse conditions. We believe that our studies will reveal important insight into general principles of plant-microbe interactions, and thus offer new effective approaches to controlling plant health and growth in sustainable agriculture.

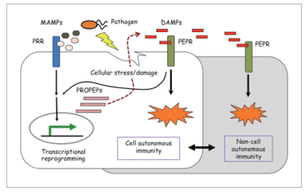


Fig. 1 Layered MAMP- and DAMP-receptor signaling provides an important basis for pathogen resistance.

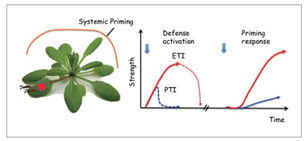


Fig. 2 Transcriptional reprogramming and priming in plant immunity. Following the initial defense activation (left arrow) upon recognition of pathogen-associated patterns (PTI) or effectors (ETI), defense-related genes become primed to allow faster and/or greater responses upon second stimulation (right arrow). Histone modifications provide a basis for this immune memory that is sustained in the generation and can be inherited by the next generation.

Major Research Topics

1. Danger sensing and signaling in plant-microbe interactions

2. Transcriptional reprogramming and priming in plant immunity

3. Coordination of plant immunity and growth in fluctuating environments

4. Endophytic and pathogenic microbes in plants

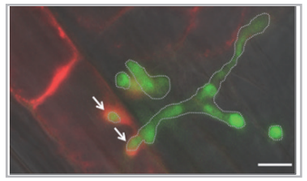


Fig. 3 Root colonization of endophyte Colletotrichum tofieldiae (Ct). Confocal microscope images of Ct constitutively expressing cytoplasmic GFP (green, labeled by dotted lines) and A. thaliana expressing VAMP722-mRFP (Red). Intracellular hyphae inside a root cortical cell are enveloped by PIP2A-mCherry-labeled host membranes (arrows). 8 day post inoculation. Bar = 10 μm.

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Laboratory Plant Symbiosis

▶ URL: http://bsw3.naist.jp/eng/courses/courses113.html


Assoc. Prof.
Satoko Yoshida

E-mail satokoy@bs.naist.jp

Outline of Research and Education

Parasitic plants - major agricultural constrains in the world

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

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

Major Research Topics

1. Identification of genes involved in haustorium formation

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

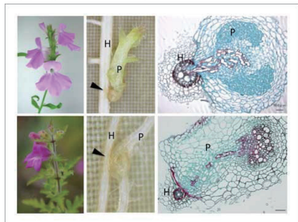

Fig. 2 Obligate parasite Striga hermonthica (upper panels) and facultative parasite Phtheirospermum japonicum (lower panels). Photos of flowers (left), host invading parasitic plant root (middle) and cross section of haustorium (right). H: host, P: parasite. Arrowheads indicate haustoria.

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

Parasitic plants recognize their hosts via small-molecular weight compounds secreted from the host plant (Fig. 4). For example, the obligate parasite *Striga* germinates in response to the plant hormone strigolactone, and its haustorium formation is induced by derivatives of cell wall lignin. However, some of our ***P. japonicum*** mutants do not respond to the known cell wall-derived chemicals, but are still able to form haustoria and parasitize hosts. We are trying to identify novel haustorium inducing compounds.

3. Comparative genomics of parasitic plants

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

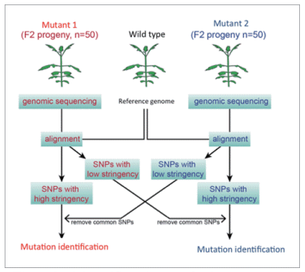

Fig. 3 Identification of the mutant causal genes using a next-generation sequencer

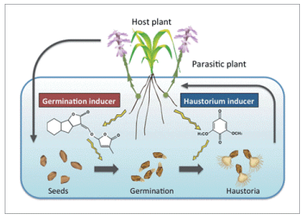

Fig. 4 Chemical communication between host and parasitic plants

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Laboratory Molecular Signal Transduction

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


Prof. Hiroshi Itoh


Assist. Prof. Tetsuo Kobayashi


Assist. Prof. Noriko Kaji

E-mail { hitoh, kobayt, nkaji }@bs.naist.jp

Outline of Research and Education

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

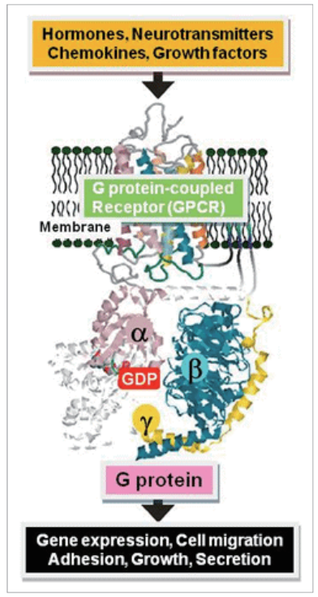

Fig. 1 Signal transduction mediated by G protein-coupled receptor

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

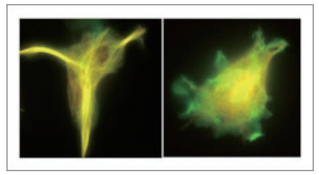

Fig. 2 G protein/PKA signal-regulated dynamics of cytoskeleton in neuronal progenitor cells

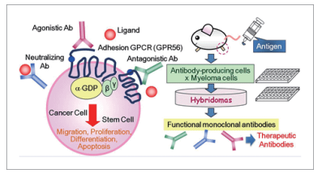

Fig. 3 Monoclonal antibody against orphan GPCR as a tool for signal analysis

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Laboratory Functional Genomics and Medicine

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


Assoc. Prof. Yasumasa Ishida


Assist. Prof. Nanaho Fukuda

E-mail { ishiday, nanahof }@bs.naist.jp

Outline of Research and Education

Since completion of the genome sequencing of a variety of organisms including mice and humans, a main task has become elucidating the functions of the sequenced genomes. For this purpose, biomedical researchers inactivate particular genes of interest in mice and analyze the phenotypes of the mutated animals, thereby revealing the functions of the inactivated genes. We will devote our efforts to the investigation on the higher cognitive functions in the immune and nervous systems in mice and humans.

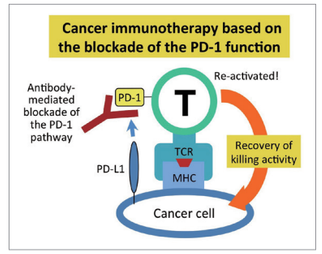

Fig. 1 Modulation of the PD-1 activity leads to effective T-cell immunity against cancer cells.

Major Research Topics

1. Elucidation of the physiological functions of PD-1

Since the discovery of PD-1 by Y. Ishida et al. in 1992, the negative immuno-regulatory functions of the PD-1 molecules expressed on the surface of activated T lymphocytes have been described. Recently, cancer immunotherapy based on the blockade of the PD-1 pathway has been successfully performed in clinics (Cell 162, 937, 2015). We try to elucidate the yet undiscovered functions of PD-1 in the self-nonself discrimination of the immune system.

2. mRNA localization in mouse sensory neurons

mRNA localization is a widely employed mechanism to target protein synthesis to specific cellular sites. It is particularly important for neuronal development and function. In mammalian olfactory sensory neurons, odorant receptor (OR) mRNAs are localized in the axon terminal. We currently investigate the molecular mechanisms of the OR mRNA localization in mouse olfactory sensory neurons and we have revealed the involvement of RNA binding proteins. We also explore how mRNA localization contributes to physiological functions and/or development of the olfactory tissue by using transgenic and knockout mouse models.

3. 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 named UPATrap that is based on the suppression of NMD, and allows for such difficult gene disruption for the first time. We are upgrading 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.

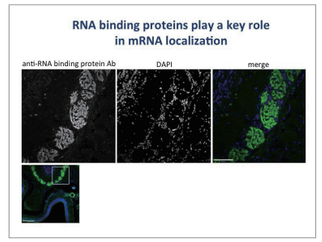

Fig. 2 Immunostaining of an RNA binding protein on the section of mouse olfactory tissue. We have found that some RNA binding proteins are highly enriched in the glomeruli of the olfactory bulb, where the axon terminal of olfactory sensory neurons exist.

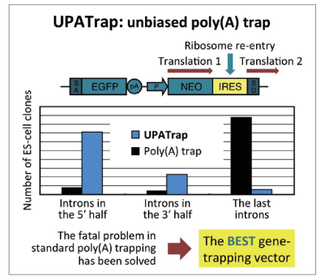

Fig. 3 The UPATrap method for the random insertional mutagenesis of transcriptionally silent genes in target cells.

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Laboratory Tumor Cell Biology

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

Prof. Jun-ya Kato
Assist. Prof. Takashi Yokoyama
E-mail { jkata, yokoyama-t }@bs.naist.jp

Outline of Research and Education

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

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

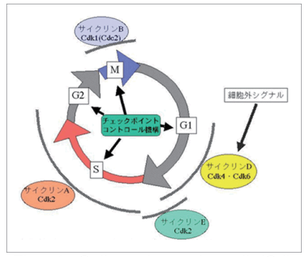

Fig. 1 Cell cycle and cyclin/Cdk complexes

Major Research Topics

1. Cell cycle control and oncogenesis

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

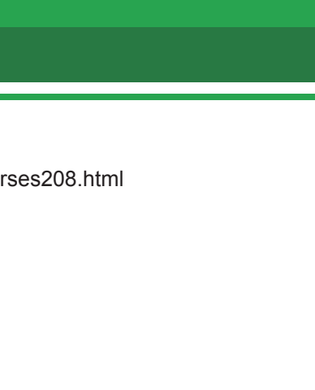

Fig. 2 A group of erythrocytes and leukocytes (upper), neutrophils (lower left) and macrophages (lower right), which were induced to differentiate from ES cells in vitro

2. Leukemogenesis

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

3. Hematopoietic stem cells

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

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

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Laboratory Molecular Immunobiology

▶ URL: http://bsw3.naist.jp/eng/courses/courses209.html

Prof. Taro Kawai
Assist. Prof. Takumi Kawasaki
Assist. Prof. Daisuke Ori
E-mail { tarokawai, kawast01, dori }@bs.naist.jp

Outline of Research and Education

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

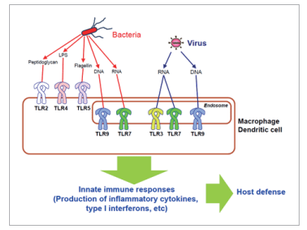

Fig. 1 Recognition of microbial components by Toll-like receptors (TLRs)

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.

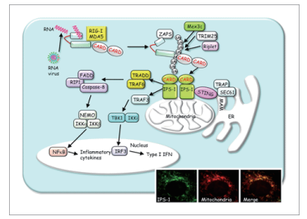

Fig. 2 Signaling pathways through RLRs, cytosolic sensors for RNA viruses

2. Analysis of RLRs

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

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

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

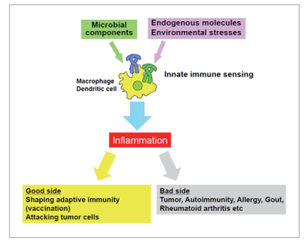

Fig. 3 Recognition of non-infection agents by innate immunity and its relevance in diseases

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Laboratory Applied Immunology

▶ URL: http://bsw3.naist.jp/eng/courses/courses213.html

Prof. Reiko Shinkura
Assist. Prof. Keiko Nakanishi
E-mail { rshinkura, knakanishi }@bs.naist.jp

Outline of Research and Education

The immune response has evolved to protect us from pathogenic infectious agents and toxic foreign substances. In acquired immune response, antigen stimulation of B cells induces two distinct genetic alterations in the immunoglobulin (Ig) loci: somatic hypermutation (SHM) and class switch recombination (CSR), both of which require an enzyme, activation-induced cytidine deaminase (AID). After these processes, among diversified Ig repertoire, selected high-affinity Igs efficiently defend the host. AID plays a crucial role in host defense but it introduces DNA cleavage into Ig loci and aberrantly into non-Ig loci causing lymphoma. Our aim is to answer the question, 'How does AID activity specifically target Ig loci?', using AID mutant protein and mutant knock-in mice, and to understand the precise molecular mechanisms of SHM and CSR.

Recently dysbiosis (gut commensal microbial imbalance) is being frequently reported to be associated with illnesses such as inflammatory bowel disease (IBD), obesity, cancer, etc. We found that the high-affinity intestinal IgA produced by SHM is important to control non-pathogenic gut bacteria as well as pathogens. Our main focus is on how intestinal IgA recognizes and targets a huge variety of gut bacteria. We have isolated a useful monoclonal IgA to modulate gut microbiota leading to symbiosis (balanced host-microbial relationship in gut).

We aim to apply the findings of our basic research to practical medicine.

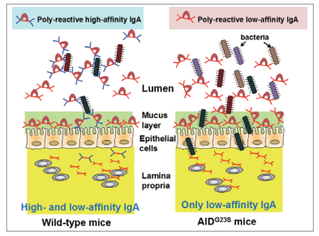

Fig. 1 Two types of intestinal IgA: poly-reactive high-affinity IgA and poly-reactive low-affinity IgA. High-affinity IgA is important to control gut lumen microbiota and prevent their invasion.

Major Research Topics

1. Mechanisms of gut microbial regulation by intestinal IgA

We generate hybridomas from IgA producing cells in the small intestines of wild type mice. We selected W27 monoclonal IgA as a best gut microbial modulator because of its strong ability to bind specifically against colitogenic bacteria. We are analyzing the bacterial target molecule for W27 to control microbial communities, and will elucidate the reason IgA selects that target from a physiological point of view. We aim to develop a therapeutic W27 IgA antibody.

2. Molecular mechanism of SHM

We have found that an N-terminal mutant AID (G23S; glycine to serine mutation at the 23rd AA) showed defective SHM but relatively intact CSR both in vitro and in vivo, suggesting the N-terminus of AID may be the domain responsible for SHM-specific co-factor binding. By investigating the SHM-specific co-factor, we will elucidate the mechanism by which AID distinguishes SHM from CSR.

3. Search for IgA CSR inducer

Upon antigen stimulation, B cells can undergo CSR to IgG, IgE or IgA isotypes. However, what induces B cells to each specific isotype is not completely understood. We focus on uncovering a novel IgA CSR inducer, which may drive IgA CSR instead of IgE CSR at the mucosal surface, helping prevent allergies, as well as enhancing mucosal immunity.

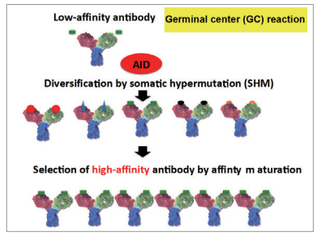

Fig. 2 In germinal center (GC) reaction, AID introduces random point mutations in the variable region sequence of Ig genes to diversify its repertoire. As a result, only high-affinity Ig producing B cells are selected in GC.

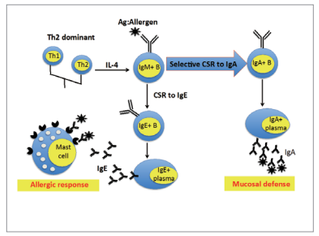

Fig. 3 Selective CSR to IgA can prevent allergic response as well as enhance mucosal defense against a given antigen.

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Laboratory Molecular Medicine and Cell Biology

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

Prof. Shiro Suetsugu
Assist. Prof. Kyoko Hanawa
E-mail { suetsugu, hanawa }@bs.naist.jp

Outline of Research and Education

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

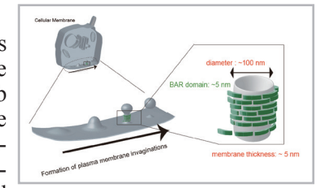

Fig. 1 Location of BAR domain functions in cells. The BAR domains function as polymers at submicron-scale invaginations, such as clathrin-coated pits and caveolae, as well as in protrusions, including filopodia and lamellipodia. The typical scales for clathrin-coated pits and caveolae are 100-200 nm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

Major Research Topics

1. Elucidating cell-shape dependent intracellular signaling

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

2. Searching for new membrane binding proteins

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

3. The importance of fatty acids in the membrane

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

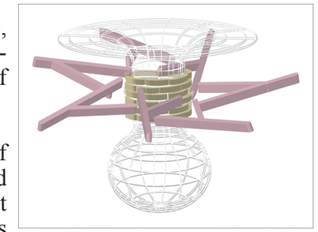

Fig. 2 Wire-frame model of the clathrin-coated pit. The BAR proteins are shown in yellow, and the actin cytoskeleton is shown in magenta. The membrane is in wire-frame. The actin filaments are thought to be finely organized on the nano-scale membrane invaginations of the clathrin coated pits.

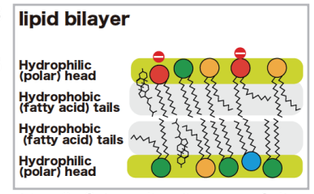

Fig. 3 Schematic diagram of the cellular membrane. Each lipid molecule consists of one hydrophilic head and two hydrophobic fatty-acid tails. There are varieties of combinations of the head, such as serine, ethanolamine, etc., and various saturated and unsaturated fatty acids, such as palmitic acid (saturated),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

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Laboratory Developmental Biomedical Science

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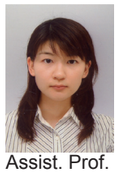
Assoc. Prof.
Noriaki Sasai



Assist. Prof.
Akiko Nishi-Hori

E-mail { noriakisasai, akikonishi }@bs.naist.jp

Outline of Research and Education

One of the central questions of classical developmental biology is to understand how a limited number of genes produce a diversity of cell types. The developing central nervous system is composed of a number of different cell types, and we seek to elucidate the molecular mechanisms leading to this diversity by employing chick and mouse embryos as model organisms.

We are also interested in the homeostasis of functional neurons. We have been utilising the model mice that have been shown to develop particular inherited retinal diseases, and propose novel therapeutics for these related dystrophies.

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

Major Research Topics

1. Transition of the intrinsic characteristics of neural progenitor cells during development and pattern formation

The neural tube is the embryonic tissue of the central nervous system, where a number of functional neurons are produced and precisely assigned. This pattern formation is mainly governed by a handful of extracellular molecules including BMP, Wnt and Sonic Hedgehog (Shh). These molecules are collectively called morphogens, and induce different neuronal subtypes in a graded manner. On the other hand, the intrinsic characteristics of neural progenitor cells change over time, and respond to the same inducing molecules differently. We are particularly interested in the relationship between the inducing activity and the cells' mode of response.

2. Detailed analysis of the Shh signalling pathway

There are many unique aspects of the intracellular signalling pathway induced by Shh. For instance, the Shh pathway is introduced into the cells through the protrusive structure on the surface of cells, called cilium. In addition, Shh target genes start to be expressed only after 6 hours, which is much slower than other signalling pathways. We attempt to identify the proteins that regulate the speed of the signal transduction, and further to reveal the relationship between the speed of the signal and the patterning of the neural tube.

3. Homeostasis of functional cells

How functional cells are maintained is also an important question. We recently demonstrated that the membrane protein Prominin-1 (Prom1) has an essential role in maintaining established photoreceptor cells, and that Prom1-deficient mice show severe retinal degeneration. In addition, our recent study suggests that Prom1 is involved in many more dystrophies in a number of other organs. We therefore aim to propose a novel therapeutic method by analysing these model mice.

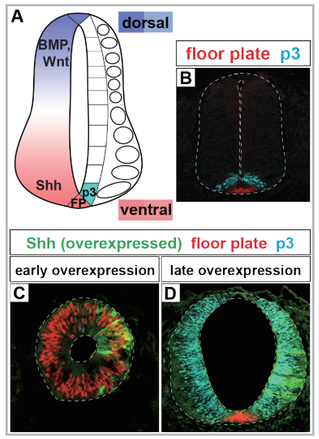


Fig. 1 (A) The cross section of the trunk neural tube. The neural tube is divided into at least 13 subdomains along the dorsal-ventral axis. (B) The floor plate and the p3 interneuron progenitor domains can be separated by immunohistochemistry. (C,D) The phenotype of the neural tube upon forced expression of Shh. The neural progenitor cells tend to differentiate into the floor plate cells (C), while they differentiate into the p3 cells when Shh is overexpressed at the late stage (D). This finding suggests that the neural progenitor cells respond to the same signal differently over time.

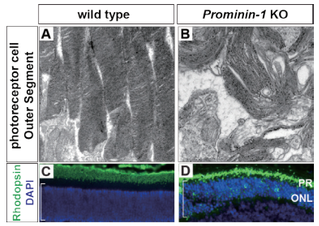


Fig. 2 Eye phenotype in the Prominin-1 (Prom1) deficient mice. The outer segments are degenerated (A,B), and Rhodopsin proteins are misplaced in the photoreceptor cells of the Prom1-knockout eyes (C,D).

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Laboratory Organ Developmental Engineering

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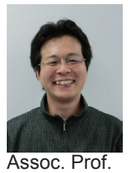

Assoc. Prof.
Ayako Isotani

E-mail isotani@bs.naist.jp

Outline of Research and Education

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

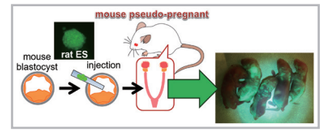

Fig. 1 Production of xenogeneic chimera
GPFP-expressing rat ES cells were injected into mouse blastocysts (mouse←rat ES chimera). We could obtain viable mouse←rat ES chimeras upon transplantation into the mouse uterus.

Major Research Topics

1. Model of organ formation using xenogeneic chimeras

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

2. Trials of novel animal models

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

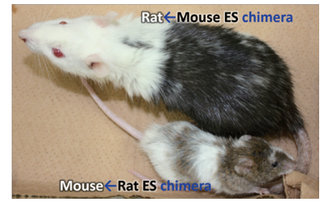

Fig. 2 Two kinds of mouse and rat xenogeneic chimeras
A rat-sized xenogeneic chimera which produced mouse ES cells injected into rat blastocysts (upper). A mouse-sized xenogeneic chimera which produced rat ES cells injected into mouse blastocysts (bottom).

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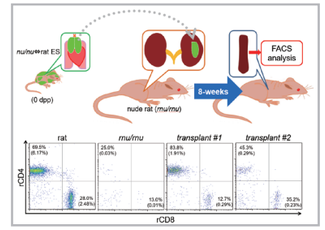

Fig. 3 The function of rat thymus in xenogeneic chimera
When rat thymus from a xenogeneic chimera was transplanted into renal subcutaneous tissues of nu/nu rat, rat T-cells were educated.

Laboratory Microbial Molecular Genetics

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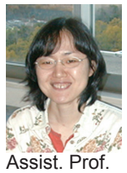
Prof.
Hisaji Maki


Assoc. Prof.
Masahiro Akiyama


Assist. Prof.
Asako Furukohri

E-mail { maki, akiyamam, furukori }@bs.naist.jp

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 also put strong emphasis on 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 assist our laboratory members in becoming globally active individuals who act and think independently.

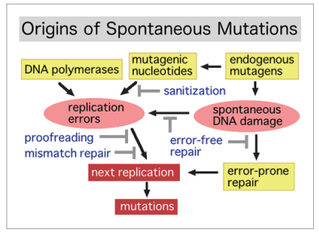


Fig. 1 Multiple mechanisms suppress mutations. However, spontaneous DNA lesions serve as major causes of mutation under normal growth conditions.

Major Research Topics

1. Mechanisms of 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, 10-12 & 14)
- Replication fork arrest and its recovery processes (Reference 10)
- Dynamics of replication fork movement on genomes (References 6, 9, 13 & 15)

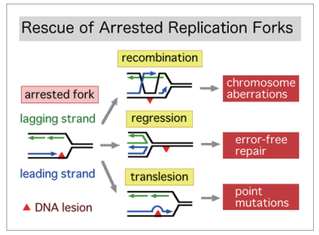


Fig. 2 When DNA replication occurs without repair of DNA lesions, replication fork progression is inhibited, potentially leading to genetic instability. Mechanisms to rescue arrested forks include recombination, regression of forks and translesion DNA synthesis.

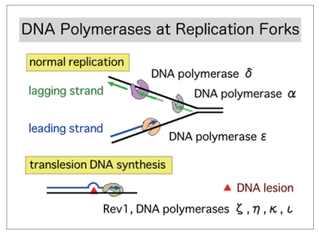


Fig. 3 Multiple DNA polymerases ordinarily work together for efficient DNA replication, thereby suppressing replication errors. Special DNA polymerases work in both eukaryote and bacteria to copy damaged DNA (translesion DNA synthesis).

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Laboratory Systems Microbiology

▶ URL: http://bsw3.naist.jp/eng/courses/courses302.html


Prof.
Hirotada Mori


Assist. Prof.
Ai Muto

E-mail hmori@gtc.naist.jp, muto@bs.naist.jp

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 the 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 characteristic 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 goal is to design genome-sized DNA molecules within constructed vectors and establish transfer systems to conjugate them into target micro-organisms.

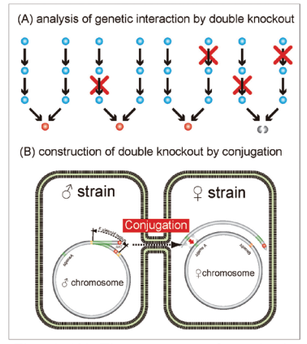

Fig. 1 (A) The concept of synthetic lethal/sickness analysis: Red circles represent essential metabolites for cells. If cells have redundant routes to produce essential metabolites, double deletion methods may identify such redundant steps of genes (enzymes). (B) The conjugation method to generate double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

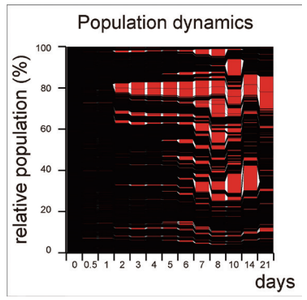

Fig. 2 The X axis shows time points of samplings and the Y axis represents population ratio of all deletion strains.

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

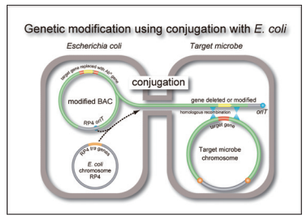

Fig. 3 Wide host-range incP family plasmid RP4 can deliver large plasmid DNA by cross-species conjugation.

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Laboratory Cell Signaling

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Prof.
Kaz Shiozaki


Assist. Prof.
Hisashi Tatebe

E-mail { kaz, htatebe }@bs.naist.jp

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 humans. Students in our laboratory are encouraged to design multifaceted approaches that logically combine research tools in molecular genetics, cell biology and biochemistry. Originally established in 1998 at University of California-Davis, our laboratory has been training researchers that serve the international scientific community.

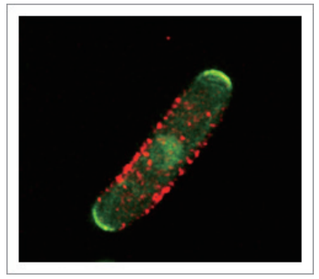
Fig. 1 Fission yeast *Schizosaccharomyces pombe*

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.

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.

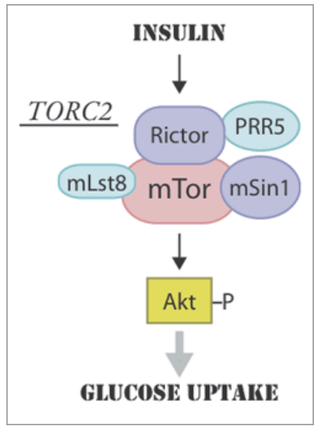

Fig. 2 TOR complex 2 (TORC2) mediates insulin signals that induce cellular uptake of glucose.

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Laboratory Applied Stress Microbiology

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


Prof.
Hiroshi Takagi


Assist. Prof.
Daisuke Watanabe


Assist. Prof.
Ryo Nasuno

E-mail { hiro, d-watanabe, r-nasuno }@bs.naist.jp

Outline of Research and Education

Our research involves “Applied Molecular Microbiology”. Our laboratory aims at basic studies in microbial science, particularly cellular response and adaptation to environmental stresses, and its 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. Novel findings from our basic studies may be applied to the breeding of useful microbes (yeasts, bacteria), the production of valuable biomaterials (enzymes, amino acids) and the development of promising technologies (bioethanol, etc.).

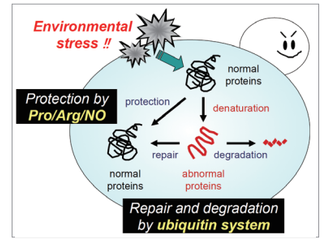

Fig. 1 Novel stress-tolerant mechanisms in *S. cerevisiae*

Major Research Topics

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

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

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

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

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

3. Metabolic regulation and physiological roles of cysteine in *Escherichia coli*

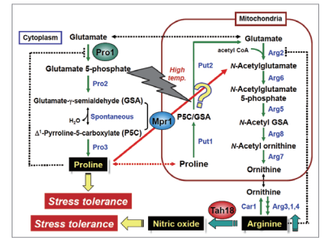

Fig. 2 Metabolic pathway of proline and arginine in *S. cerevisiae*

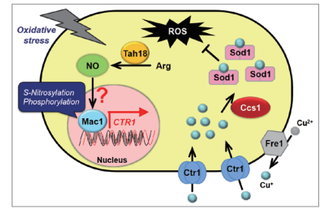

Fig. 3 NO-mediated antioxidative mechanism in *S. cerevisiae*

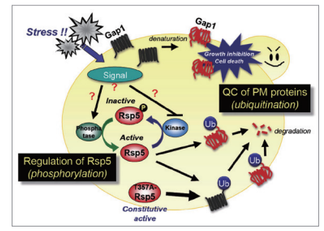

Fig. 4 Ubiquitin system under stress conditions in *S. cerevisiae*

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Stress response and tolerance in yeast *Saccharomyces cerevisiae*

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Development of industrial yeast based on novel stress-tolerant mechanisms

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Laboratory Structural Biology

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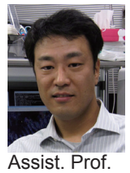

Prof. Toshio Hakoshima
Assist. Prof. Ken Kitano
Assist. Prof. Tomoyuki Mori

E-mail { hakosima, t-mori }@bs.naist.jp, kkitano@is.naist.jp

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 and, in turn, unable to 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 overall goal is to contribute to the 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 expect our lab to be an international one and we welcome foreign students to study protein structures and functions with us.

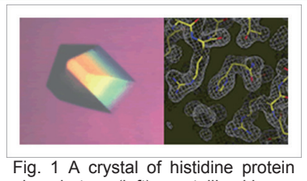

Fig. 1 A crystal of histidine protein phosphatase (left), crystallized in our laboratory and part of its electron density map at 1.9 Å resolution obtained from X-ray crystal structure analysis

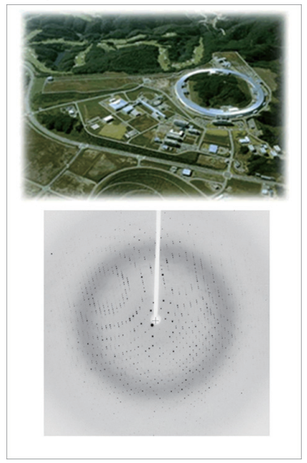

Fig. 2 The SPring-8 synchrotron radiation facilities at Harima, Hyogo. We perform X-ray intensity data collection at SPring-8 for structure determination.

Major Research Topics

1. Structural molecular medicine

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

2. Structural cell biology

G proteins, and 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

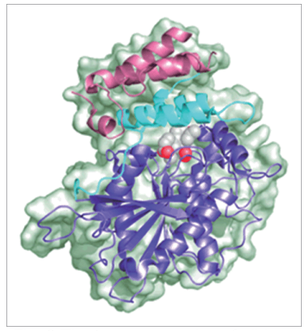

Fig. 3 The ternary complex of gibberellin (space-filled model in white and red)-bound receptor GID1 (blue and cyan) trapping its downstream effector protein DELLA protein (pink) from our recent Nature article [4]

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Laboratory Membrane Molecular Biology

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Assoc. Prof. Tomoya Tsukazaki
Assist. Prof. Yoshiki Tanaka

E-mail { ttsukaza, yotanaka }@bs.naist.jp

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 have enabled us to propose conformational changes of Sec proteins during protein translocation. However, the details of the molecular mechanisms remain unclear. Sec structures of other forms and at high resolution are required to fully understand Sec protein translocation processes. 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 mechanisms of various materials including drugs.

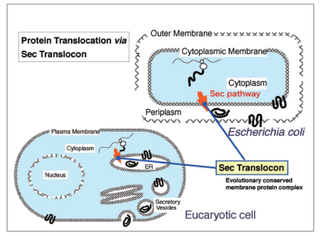

Fig. 1 Conserved protein translocation across the membrane

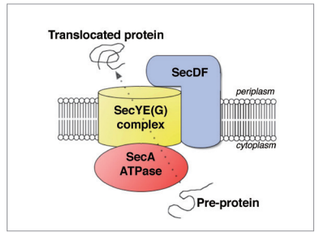

Fig. 2 Bacterial Sec machinery. SecYEG complex provides the pore for protein movement that is driven by two motors, SecA and SecDF.

Major Research Topics

1. Protein transport across cell membranes

2. Molecular function and dynamics of membrane proteins

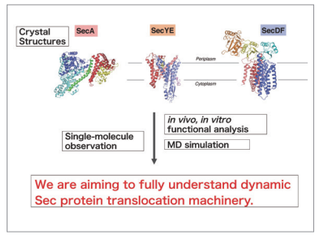

Fig. 3 Our strategy for visualizing protein translocation

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Laboratory Gene Regulation Research

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


Prof.
Yasumasa Bessho


Assoc. Prof.
Takaaki Matsui


Assist. Prof.
Yasukazu Nakahata

E-mail { ybessho, matsui, yasu-nakahata }@bs.naist.jp

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.

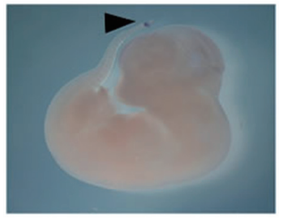
Fig. 1 Transcription factor Hes7, serving as a molecular clock, is specifically expressed in the primordium of somites.

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 mid-embryogenesis. Somites are symmetrically arranged on both sides of the neural tube as even-grained epithelial spheres that give rise to vertebrae, ribs, muscles and skin.

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

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

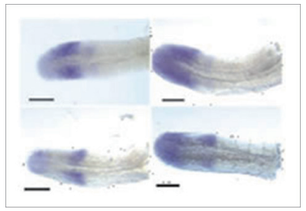
Fig. 2 The expression of Hes7 oscillates in the primordium of somites.

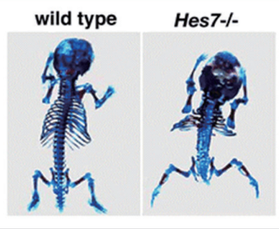

Fig. 3 In Hes7 knockout mice, somite segmentation does not occur cyclically and the metameric structures along the anteroposterior axis are lost.

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Laboratory Systems Neurobiology and Medicine

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


Prof.
Naoyuki Inagaki


Assist. Prof.
Akihiro Urasaki


Assist. Prof.
Michinori Toriyama

E-mail { ninagaki, aurasaki, toriyama }@bs.naist.jp

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 this miraculous phenomenon of 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 loops and lateral inhibition may be involved, but how do 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 inhomogeneous 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 Shootin1a, Shootin1b and Singar1, which we identified via proteome analyses. We analyze the molecular mechanisms for cell migration, neuronal polarization, axon guidance and synaptogenesis, using up-to-date methods including systems biology and mechanobiology. We expect that these analyses will give us a new window into therapeutic strategies for nerve injury, Alzheimer’s disease and cancer metastasis.

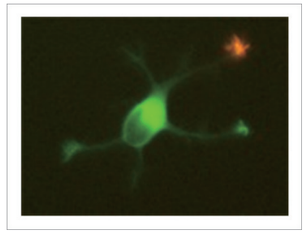
Fig. 1 Shootin1 is a key molecule involved in neuronal symmetry breaking.

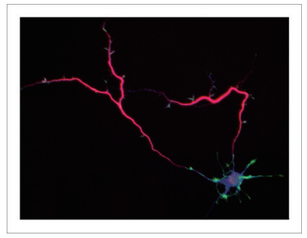
Fig. 2 Singar knockdown leads to formation of surplus axons.

Major Research Topics

1. Molecular mechanisms of neuronal network formation
2. Generation of mechanical forces for axon guidance and neuronal migration
3. Sensing of cellular length and size
4. Actin waves and novel mechanisms of protein transport
5. Brain morphogenesis and diseases

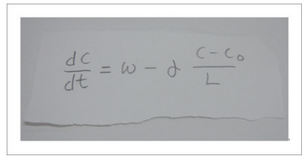

Fig. 3 An equation to describe neurite length sensing by shootin1

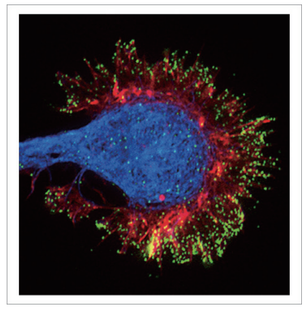
Fig. 4 Signal-force transduction through shootin phosphorylation at growth cones

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Laboratory Humanophilic Innovation Project

▶ URL: http://bsw3.naist.jp/eng/courses/courses903.html

Prof.
Taku Demura

Assoc. Prof.
Minoru Kubo

Information Science
Prof. Keiichi Yasumoto
Assoc. Prof. Yutaka Arakawa

Materials Science
Prof. Jun Ohta
Prof. Yukiharu Uraoka

E-mail { demura, ku-bo }@bs.naist.jp

Outline of Research and Education

We promote seminal research for the creation of human life support systems in the "Humanophilic Innovation Project". With this approach, we endeavor to create novel interdisciplinary research integrating the fields of material, biological and information science, and to produce researchers and engineers capable of solving the complicated problems facing the world and in the future. These achievements will be applied to develop new support systems for social activities such as agriculture and nursing care, in order to address the needs created by a low birth rate and an aging population.

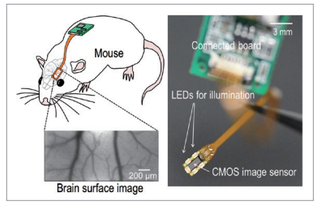

Fig. 1 Development of monitoring technology for biological activity. Monitoring brain activity and action of a mouse with a micro photonic device.

Major Research Topics

1. Development of monitoring technology for biological activity
- Development of micro photonic device systems for organisms
- Application of monitoring technology with portable devices

2. Development of ecological device systems
- Construction of nano devices using organic super molecules
- Production of green materials using synthetic biology

3. Creation of human life support systems
- Application of ubiquitous computing systems
- Integration of achievements of monitoring technology and ecological device systems

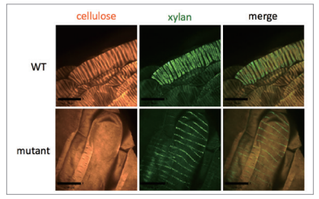

Fig. 2 Development of ecological device systems. Micrographs of a cell wall of Arabidopsis mutant's modified production of cellulose as a green material by genome breeding.

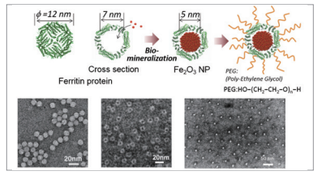

Fig. 3 Development of ecological device systems. Controlling density of the organic super molecule ferritin for development of new eco devices.

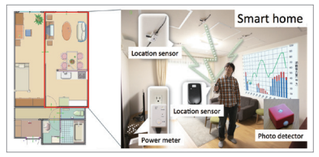

Fig. 4 Creation of human life support systems. Demonstration of a context awareness system and monitoring of human activity in a "smart home".

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Affiliate Laboratory Molecular Genetics of Human Diseases

(with Osaka Medical Center for Cancer and Cardiovascular Diseases)

▶ URL: http://bsw3.naist.jp/eng/courses/courses501.html

Affiliate Assoc. Prof.
Yoji Kukita

E-mail katou-ki@mc.pref.osaka.jp

Outline of Research and Education

Our recent research focus is circulating tumor DNA (ctDNA), which is cell-free DNA released from dying cancer cells (Fig. 1). Because ctDNA enables detection of cancer cell DNA of various lesions using only a small amount of blood (~ 1 ml), there are huge expectations for clinical applications including early detection. We use next-generation sequencing (NGS) to detect ctDNA. We offer students the opportunity to study experimental basics and bioinformatics of NGS.

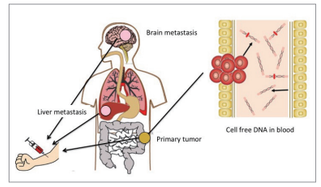

Fig. 1 Circulating tumor DNA

Major Research Topics

1. Noninvasive genotyping of *EGFR* for lung cancer therapy

Gefitinib (Iressa) is a molecular target agent for lung cancer to inhibit tyrosine kinase activity of *EGFR*. It is effective only for lung cancer with activating *EGFR* mutations, and patients are selected through a genetic test. Gefitinib is a good example of "personalized medicine" (Fig. 2), a new concept of medicine, i.e., choosing therapy based on genetic information of each patient. An important concern in clinical practice is that tumor samples are often difficult to obtain by biopsy. In particular, biopsy for advanced or resistant cases and repeated sampling is extremely difficult.
We developed a noninvasive detection system for *EGFR* mutation in ctDNA based on NGS (Kukita et al., 2013). The mutations are sought in more than 100,000 reads of the *EGFR* fragments. We conducted a multi-institute prospective study to evaluate the performance of the detection system, and demonstrated that the system was sufficient for practical use (Uchida et al., 2015). This study was done in collaboration with the Department of Thoracic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases.

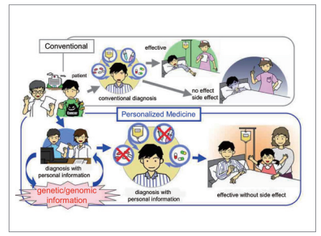

Fig. 2 Personalized medicine

2. Development of methodologies for cancer detection

The accuracy of current sequencing technologies has limitations when detecting rare mutations in multiple loci. To overcome this problem, we developed a new sequencing method named NOIR-SeqS (non-overlapping integrated read sequencing system) (Fig. 3) (Kukita et al, 2015). The system employs the barcode technology, and achieved 60-100 fold increase of accuracy from that of the standard NGS. We applied NOIR-SeqS to ctDNA, demonstrating its feasibility for practical use.

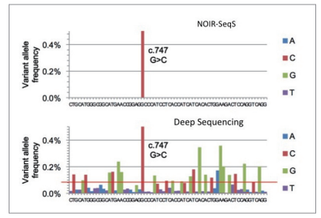

Fig. 3 Detection of a mutation in TP53. Top, NOIR-SeqS; bottom, conventional next-generation sequencing

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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

Affiliate Assoc. Prof.
Takashi Nishimura
E-mail t-nishimura@cdb.riken.jp

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 times 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.

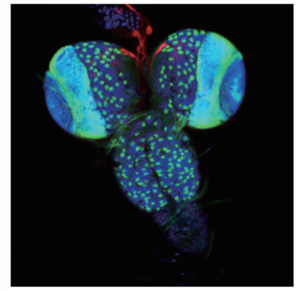

Fig. 1 Larval central nervous system in Drosophila. Neural stem cells (green) and insulin-producing cells (red) are shown.

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

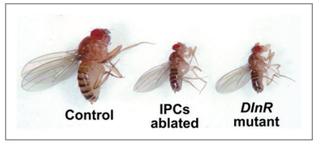

Fig. 2 Drosophila mutants defective for systemic growth. Down regulation of the insulin signaling leads to the formation of small flies. The picture shows brain insulin-producing cell (IPCs) ablated flies and Drosophila insulin receptor (DInR) mutant flies.

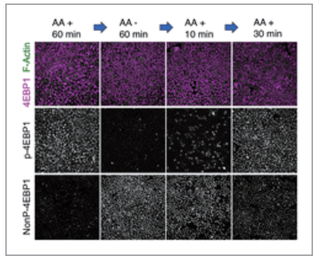

Fig. 3 Amino acid response in cultured mammalian cell lines. The phosphorylation level of 4EBP1, a downstream target of the TOR kinase, is used as a readout of amino acid (AA) dependent activation of the TOR. Top panels indicate total 4EBP1 levels. Middle panels indicate phosphorylated 4EBP1, while lower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

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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

Affiliate Prof.
Masayuki Inui
E-mail mmg-lab@rite.or.jp

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 functions to tackle the adverse effects of global climate change and mitigate energy supply problems is carried out in our laboratory.

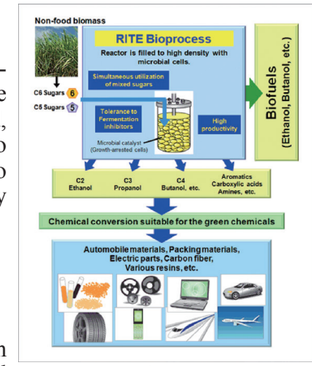

Fig. 1 The biorefinery concept

Major Research Topics

1. Biorefinery

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

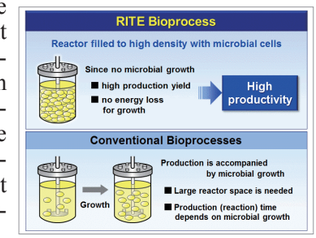

Fig. 2 Novel features of the RITE Bioprocess

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.

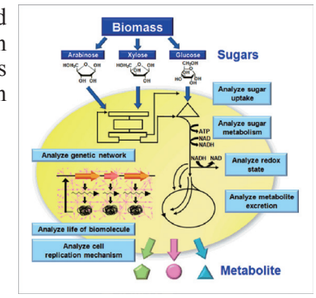

Fig. 3 Breeding of recombinant strains using system biology

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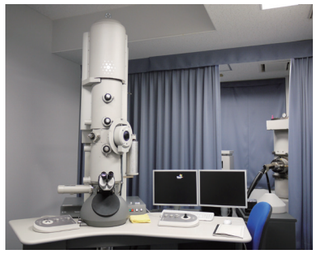
Graduate School of Biological Sciences

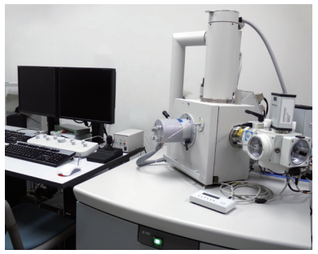
Research Facilities and Equipment

Abundant Research Facilities

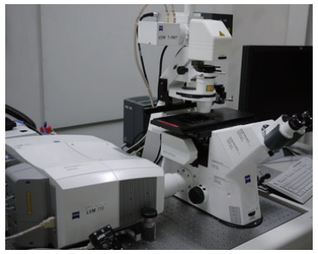
Each division is equipped with a variety of state-of-the-art equipment.
Shared equipment, among the most advanced available for biological science research in Japan,
is provided at numerous locations within the school.



Transmission Electron Microscope

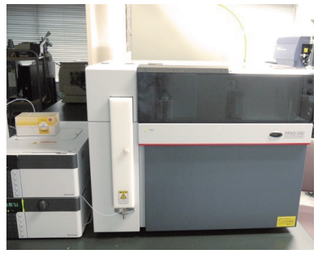


Scanning Electron Microscope

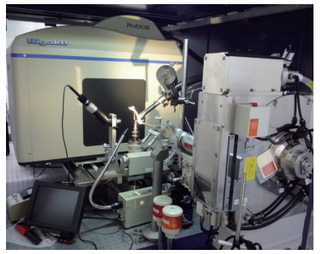


Confocal Laser Scanning Microscope

Triple Quadrupole Mass Spectrometer



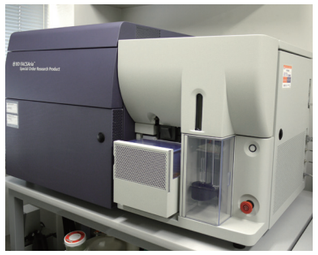
Protein Sequencer



Ultra High-Intensity Microfocus X-ray Generator·Macromolecular Crystallography Diffraction System

High Resolution Fluorescence Microscopy Imaging System

Molecular Interaction Analysis System

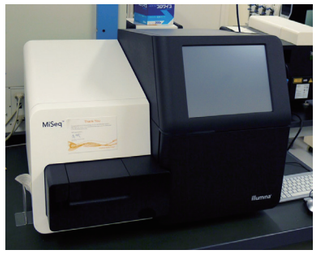


Flow Cytometer

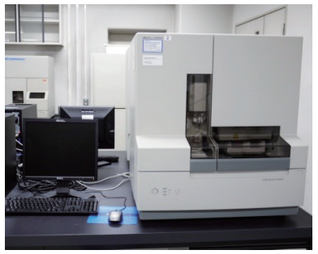
Cell Preservation Container

Botanical Greenhouse

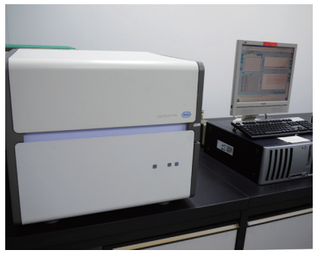
Animal Experimentation Facility



Next Generation Sequencer



DNA Sequencer



Real-Time PCR System

Radioisotope Facility