Proteostasis

Understanding proteostasis and discovering innovative medical applications

Research and Development Objectives

Understanding and medical application of proteostasis

This R&D area aims to clarify the relationship between structure and function based on evidence obtained from biochemical and structural biological approaches, to understand the molecular pathways that cause various diseases, and to discover potential solutions for healthcare or methods to maintain good health. The R&D is focused on understanding the molecular basis of proteins during the processes that occur between initial protein translation and synthesis to ultimate degradation, and will investigate denaturation, aggregation, and degradation processes that set proteins on a final, irreversible pathway, as well as posttranslational modifications that have irreversible effects on protein function. Target diseases include, but are not limited to, neurodegenerative disease, mental health disorders, intractable cancers, chronic inflammatory diseases, amyloidosis, fibrosis, rare diseases, infectious diseases, and lifestyle diseases like arteriosclerosis and diabetes, as well as insights into how to avoid aging and maintain a healthy state. As well as researchers involved in the fields of proteins and glycans, we welcome participation by basic science or clinical researchers in structural biology, immunity, metabolism, or nerve systems, as well as researchers from other fields, including analytical chemistry and bioinformatics. The goal is to make progress in world-class, highly innovative research and development by bringing together and leveraging the strengths of a range of disciplines.

Program Supervisor (PS)

NAGATA Kazuhiro

Director General,
JT Biohistory
Research Hall

Program Officer (PO)

ENDO Tamao

Senior Fellow, Tokyo Metropolitan Institute of Gerontology

Advisor

ADACHI Takeshi
Professor, School of Medicine, National Defense Medical College

INADA Toshifumi
Professor, The Institute of Medical Science, The University of Tokyo

IWAI Kazuhiro
Provost, Executive Vice-President, Kyoto University

KATO Koichi
Professor, Exploratory Research Center on Life and Living Systems, National Institutes of Natural Sciences

KINOSHITA Taroh
Professor, Research Institute for Microbial Diseases, Osaka University

SHIMIZU Ritsuko
Professor, Tohoku University School of Medicine

SUZUKI Rami
Representative Director and CEO, ARC Therapies Inc.

FUJIMOTO Toyoshi
Research Professor, Juntendo University School of Medicine

MIYOSHI Eiji
Professor, Graduate School of Medicine, Osaka University

YAMADA Hisafumi
Former Executive Vice President, Chugai Pharmaceutical Co., LTD.

AMED-CREST Started in 2020 · 1st period

Protein aggregation and translation: yin and yang of diseased neurons

IWASAKI Shintaro
Chief Scientist,
Cluster for Pioneering Research, RIKEN

Recent years have seen growing evidence that unbalanced proteostasis leads to neurodegenerative diseases. Although studies have revealed that tight coupling between aggregation and protein synthesis is fundamental for proteostatic regulations, our understanding of the mechanism is quite poor.
Here, we aim to demystify the mutual interactions between protein aggregation and translation in diseased neurons. For this purpose, we will unveil the local translation in axon and its dysregulation in neurodegenerative diseases.

Study of mitochondrial proteostasis controlled by protein trafficking

ENDO Toshiya
Professor, Faculty of Life Sciences,
Kyoto Sangyo University

Most mitochondrial proteins are imported from the cytosol and failure in this mitochondrial protein trafficking leads to the collapse of “mitochondrial proteostasis”, which will deteriorate cellular functions and in human, eventually manifest in ageassociated diseases such as neurogenerative disorders. In this project, we will reveal the roles of protein trafficking and related quality control, including those of PINK1 and MICOS, in the mitochondrial proteostasis primarily by structural biology approaches. We will thus unveil the still elusive mechanisms of the contribution of protein trafficking to the proteostasis, which could represent new targets for preventative and/or therapeutic treatments of aging and aging-related diseases.

Cytosolic Glycobiology – Toward comprehensive understanding of the cellular homeostasis

SUZUKI Tadashi
Chief Scientist, RIKEN Cluster
for Pioneering Research (CPR)

N-Glycosylation occurs in the lumen of the endoplasmic reticulum (ER), and glycosylated proteins are delivered to their respective destinations via a secretory pathway. On the other hand, there are also phenomena in the cytosol, which is segregated from the secretory pathway by a lipid bilayer, for which N-glycans play pivotal roles. We will aim at comprehensive understanding, as well as medical application, of glycan-regulated proteostasis, with particular focuses on NGLY1, a well-conserved de-N-glycosylating enzyme, and FBS proteins, E3 ubiquitin ligase subunits that recognize N-glycans, through diverse approaches.

Study on organelle homeostasis by post-translational modifications

MATSUDA Noriyuki
Professor, Department of Biomolecular Pathogenesis,
Medical Research Laboratory, Institute of Science Tokyo

Organelle homeostasis is maintained through a cycle of biogenesis and degradation. In this process, organelles destined for degradation are distinguished by the autophagy adaptors. Recently, it has become clear that the spatiotemporal aspects of degradation are precisely controlled via coordination of the autophagy adaptors and posttranslational modifications. However, the physiological importance of this highly coordinated process and the molecular mechanisms underlying the coupling of post-translational modifications with organelle degradation are still obscure. Through this project, we aim to clarify the mechanisms underlying recognition and degradation of target organelles, the physiological roles in organelle homeostasis, and the relevance of the process in human diseases.

Study on understanding of the molecular mechanisms of tissue-specific unfolded protein responses for radical cure of human chronic diseases

MORI Kazutoshi
Deputy Director-General and Distinguished Professor,
Kyoto University Institute for Advanced Study

Social demand for development of radical cure methods to chronic diseases such as neurodegenerative diseases, nonalcoholic steato-hepatitis, and chronic kidney disease is extremely high in these days. Endoplasmic reticulum (ER) stress (accumulation of unfolded/misfolded proteins in the ER) is a key for development and progression of various chronic diseases. Therefore, all eukaryotic cells are equipped with a signaling cascade termed the unfolded protein response (UPR) to cope with ER stress We will deepen the understanding of the molecular mechanisms of tissue-specific UPRs, which will lead to paradigm shift in the understanding of unmet chronic diseases and development of radical therapy.

AMED-CREST Started in 2021 · 2nd period

Study on chemical proteostasis: novel mechanisms of protein quality control ensured by the cooperation of redox, pH and metal ions

INABA Kenji
Professor,
Medical Institute of Bioregulation, Kyushu University

Over the past decades, many scientists have studied on molecular chaperones that assist in productive protein folding, and degradation systems that eliminate misfolded proteins. Here, we aim to elucidate novel protein quality control systems ensured by three chemical parameters, namely, redox, pH, and metal ions, in the early secretory pathway comprising the ER and Golgi. To this end, we employ comprehensive approaches including structure analysis, live-cell imaging, and proteomics. We focus particularly on membrane transporters that govern these chemical parameters in cells, and elucidate the close linkage of their loss of function to diseases. In this context, we will also develop inhibitors specific to the membrane transporters.

The neo-ubiquitin code for improving proteostasis dysregulation

OHTAKE Fumiaki
Associate Professor,
Hoshi University, Institute for Advanced Life Sciences

We clarify the formation and decoding mechanisms of the "neo-ubiquitin code" responsible for the degradation of abnormal proteins such as those that cause neurodegenerative diseases. Our goal is (i) to understand the mechanism of proteostasis maintenance from the standpoint of the ubiquitin–proteasome system, and (ii) to develop a basis for chemical control of proteostasis. Using quantitative proteomics, we will elucidate the mechanism by which aberrant proteins are decorated with the neo-ubiquitin code and are delivered to the proteasome. We will also analyze proteostasis by using newly developed model mice and synthesize chemicals to degrade aberrant proteins that cause neurodegeneration.

Comprehensive study of in vivo protein folding in proteostasis network

TAGUCHI Hideki
Professor,
Institute of Innovative Research, Institute of Science Tokyo

All proteins in cells are synthesized via translation at the ribosome, folds into correct tertiary structures, and are translocated to the appropriate place to perform their function. Protein folding is essential for life as the first step in the proteostasis network. Although its disruption or perturbation is known to lead to many human diseases such as cystic fibrosis, the molecular mechanism is not well understood. This project aims to elucidate the mechanism of cotranslational folding of disease-related proteins by introducing novel experimental approaches from the reconstituted level to the cellular level and lead to novel therapeutic strategies and drug discovery.

Studies on amyloid formation and disaggregation mechanisms and medical applications for neurodegenerative diseases

TANAKA Motomasa
Team Leader,
RIKEN Center for Brain Science

Amyloid deposition in the brain is associated with many neurodegenerative diseases. Therefore, the formation and disaggregation of amyloid are the key processes for neurodegeneration including cell-to-cell propagation of amyloid. However, molecular mechanisms of amyloid disaggregation have been poorly understood due to the lack of appropriate techniques and experimental systems. To address this long-standing question in amyloid biology, we aim to decipher amyloid disaggregation process by developing new biophysical methods and less-invasive, in vivo imaging techniques. Furthermore, we will develop novel techniques for selective disaggregation and degradation of amyloid in cellular and mouse models of neurodegenerative diseases. These studies will provide important implications for therapeutic development.

Molecular basis for progressive and age-related cardiorenal damages mediated by irreversible protein methylation

FUKAMIZU Akiyoshi
Professor, Life Science Center for Survival Dynamics,
Tsukuba Advanced Research Alliance, University of Tsukuba

Heart and renal failures induced by cardiorenal damages are one of the leading cause of death in the world, and they are known to affect our quality of life (QOL). Although the modification of proteins such as methylation is required for regulating cellular actions, little is known regarding the roles for protein methylation in tissue damages. In this project, combining approaches of biochemistry, bioinformatics, and structural biology, we will unlock molecular basis for progressive and age-related cardiorenal damages mediated by irreversible protein methylation.

AMED-CREST Started in 2022 — 3rd period

Regulation and Disruption of Neuronal Circuit Formation by Glycans: Pathophysiology of Mental Disorders

KADOMATSU Kenji
Professor,
Nagoya University Graduate School of Medicine

Glycans are beginning to be understood to induce plastic changes such as synapse formation and removal by regulating protein-glycan interactions to generate structural plasticity in neurons. In this study, we will apply a new technology that enables comprehensive acquisition of glycan structures and use patient-based materials such as iPS cell-derived brain organoids to understand the neural regulatory functions of glycans in a multilevel manner and elucidate pathological conditions caused by glycan alterations through a single integrated study from genome to glycoproteins and neural circuits.

Analysis of Golgi proteostasis and its medical application

SHIMIZU Shigeomi
Professor,
Pathological Cell Biology, Institute of Science Tokyo

Golgi membrane-associated degradation (GOMED) plays a central role in Golgi proteostasis, which is a qualitative and quantitative regulation of plasma membrane proteins and secreted proteins. In this study, we will clarify where and when GOMED is executed in our body. In addition, we will conduct drug discovery and development research for diseases caused by GOMED abnormalities.

Elucidation of mechanisms underlying degradation of misfolded proteins in neurons and their role in neurodegenerative diseases

NAKANISHI Makoto
Professor, Institute of Medical Science,
The University of Tokyo

Failure of protein quality control (PQC) system promotes the accumulation of misfolded proteins and is closely associated with various age-related changes. Especially in the nervous system, the impaired PQC system is directly related to various symptoms of brain aging. In this research project, we will uncover the molecular and structural basis for selective removal of misfolded proteins. Based on these findings, we will also elucidate the pathophysiology of various age-related diseases, including neurodegenerative diseases.

Elucidation of Proteostasis Regulation by Intracellular Membrane Dynamics for Healthy Longevity

YOSHIMORI Tamotsu
Specially appointed professor, Graduate School of Medicine
Division of Health Sciences, Osaka University

The autophagy and endocytosis pathways, which transport proteins to lysosomes for degradation and recycling of proteins inside and outside the cell, are important membrane dynamics for proteostasis regulation. Abnormalities in these membrane dynamics lead to accelerated aging and shortened lifespan. This research aims to clarify the molecular background of proteostasis regulation by lysosome-associated membrane dynamics and to create seeds that will lead to the healthy longevity, thereby solving an urgent problem in our super-aging society.

PRIME Started in 2020 ····· 1st period

Phase-separation-initiated proteolysis by degraders (*)

ARIMOTO Hirokazu
Professor, Graduate School of Life Sciences, Tohoku University

Autophagy, an intracellular degradation system, contributes to the suppression of diseases and aging by removing harmful materials. In this study, we aim to create new compounds that promote the selective removal of the harmful materials through autophagy by elucidating the importance of liquid-liquid phase separation in the mechanism of selective autophagy.

The quality control mechanisms of nascent organellar proteins (*)

IZAWA Toshiaki
Associate Professor, University of Hyogo, Graduate School of Science

Accumulation of aberrant proteins is a common feature of neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease. Recent studies have revealed that aberrant proteins produced by failure of translation can be tagged at their C-terminus with multiple alanyl and threonyl residues, so called "CAT-tail". However, its function and physiological significance are poorly understood. In this study, I will uncover the roles of CAT-tail by focusing on the fate of organellar proteins and establish the molecular basis for regulation of CAT-tailing and cellular proteostasis.

Understanding of cell-type-specific proteostasis of ribosome and elucidation of novel disease development mechanism (*)

IWASAKI Mio
Junior Associate Professor, Center for iPS Cell Research and Application, Kyoto University

Diamond-Blackfananemia (DBA) is a disease caused by ribosomal protein mutations with malformations such as impaired erythropoiesis, microcephaly, and micrognathia. Multiple gene mutations have been reported in ribosomal genes for DBA disease. However, these mutations cannot be found for about 40% of DBA patients, suggesting there must be another mechanism of disease development. In this study, I focus on proteostasis of ribosomal proteins responsible for DBA disease to know a novel factor is involved in the control of the disease onset.

Development of Ultra-sensitive Quantitative Glycome Analysis Method and Elucidation of Spatial Glycostasis in Tissue Microenvironment and its Medical Application (*)

KAWAI Takayuki
Associate Professor
Faculty of Science, Kyushu University

Glycosylation is an important post-translational modification of proteins. However, there has been no standard method that achieved sensitive and quantitative profiling of glycans, hindering researches on glycobiology. In this research project, an ultra-sensitive capillary electrophoresis technique will be applied to achieve 10 zmol (6200 molecules) detectability and absolute quantitation in glycan analysis. Based on this next-generation glycome analysis, we aim to clarify unknown functions of glycans in pathogenic tissue microenvironment.

Proteostatic regulation for maintaining the function of adult neural stem cells (*)

KOBAYASHI Taeko
Associate Professor, The Institute of Medical Science, The University of Tokyo

The majority of neural stem cells in the adult mammalian brain are quiescent. Quiescence is essential for retaining adult neural stem cells for a long period, and its dysregulation contributes to a decline of brain function. I have revealed the significant involvement of lysosomes in quiescence of neural stem cells. In the current study, I aim to elucidate the molecular mechanism to control proteostasis in quiescent and proliferating neural stem cells. I focus on proteostatic changes via physical properties of extracellular environments and develop a new approach for maintaining the function of adult neural stem cells.

Use of polySia-NCAM for development of diagnosis and treatment of mental disorders (*)

SATO Chihiro
Professor, Graduate School of Bioagricultural Sciences and Institute for Glyco-Core Research, Nagoya University

The diagnosis and treatment of the mental disorder are the urgent problem worldwide. Many mental disorders-associated molecules are reported to show structural and functional abnormalities in brain. Precise understanding of the molecular mechanism of functions of those molecules would finally lead to a new drug discovery in diagnosis and treatment. Focusing on polysialylated NCAM (polySia-NCAM), whose impairments are known to be related to mental disorders, such as schizophrenia, bipolar disorder and autism, this project seeks to understand its proteostasis in normal and pathogenic states.

Study of cellular proteostasis dynamics by imaging or manipulation of proteasome activity (*)

HAMAZAKI Jun
Lecturer, Graduate School of Pharmaceutical Sciences, Tokyo University

The proteasome plays an essential role in proteostasis by the degradation of ubiquitinated proteins. In recent years, it has been known that the expression level of proteasome influences the onset of cancer or neurodegenerative diseases and lifespan in model organisms. In this project, I will establish a method to quantitatively evaluate or image cellular proteostasis level, mainly monitored by proteasome activity. Furthermore, I will establish a method to manipulate proteasome activity based on the elucidation of the regulation mechanisms of the proteasome.

Mechanism of autophagy driven by liquid-liquid phase separation (*)

FUJIOKA Yuko
Associate Professor, Institute for Genetic Medicine, Hokkaido University

Accumulation of denatured proteins in cells, which is caused by ageing, leads to onset of severe diseases such as neurodegeneration and cancer. Autophagy protects us from these diseases by degrading proteins and providing amino acids for synthesis of new proteins. In this study, I aim to elucidate the molecular mechanisms of autophagy initiation and sequestration of proteins into autophagosomes using the concept of phase separation of proteins.

Study for physiological regulation and cancer metastasis through modification with glycerol phosphate as a glycosylation termination factor of dystroglycanof dystroglycan (*)

YAGI Hirokazu
Associate Professor, Graduate School of Pharmaceutical Sciences, Nagoya City University

In our previous study, we discovered a novel post-translational modification in which the non-reducing end of a dystroglycan glycan was capped with glycerol phosphate (GroP). Such capping suggests that GroP suppresses elongation of glycan chains. More interestingly, we recently found that GroP expression was enhanced in colon cancer cells with high metastatic capability. Thus, the proposed study aims to elucidate physiological regulation and cancer metastasis through modification with glycerol phosphate operating as a glycosylation termination factor of dystroglycans. This study will also attempt to develop anticancer drugs targeting GroP.

PRIME Started in 2021 ····· 2nd period

Understanding and control of cytotoxic TDP-43 phase transition

ASAKAWA Kazuhide
Associate Professor,
National Institute of Genetics

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder characterized by progressive degeneration of motor neurons in the brain and spinal cord. A major hallmark of ALS is the deposition of cytoplasmic inclusions containing aggregates of the RNA/DNA-binding protein TDP-43. In this study, by using an optogenetically controllable TDP-43 variant, we aim to reveal the mechanisms of TDP-43 cytotoxicity and develop methods to intervene toxic TDP-43 phase transition in the motor neurons, which present a potential avenue for novel ALS therapeutics.

Ubiquitin-dependent proteasome phase separation for maintaining proteostasis

ENDO Akinori
Associate Investigator,
Department of Basic Medical Sciences,
Tokyo Metropolitan Institute of Medical Science

Proteolysis mediated by the ubiquitin-proteasome system plays an essential role in the regulation of proteostasis. It has been speculated that dysregulations in this system lead to neurodegenerative diseases, however, the direct causal relationship remains elusive. In this program, I will investigate the molecular mechanism of proteostasis regulation by ubiquitin-proteasome phase separation and evaluate the hypothesis that defects in the regulation of ubiquitin-proteasome phase separation cause neurodegenerative diseases, aiming to further understand proteostasis and establish a basis for new therapeutic strategies for neurodegenerative diseases.

Study on the novel complexed ubiquitination-regulated cell death and its involvement on the inflammatory bowel diseases

OIKAWA Daisuke
Associate professor,
Department of Medical Biochemistry, Graduate School of Medicine, Osaka Metropolitan University

Protein ubiquitination generates a variety of ubiquitin chains via seven lysine residues and N-terminal methionine residues in the ubiquitin molecule, as well as complexed ubiquitination including multiple types of linkages, such as hybrid and branched chains, and regulate a variety of cellular functions. This project aims to elucidate the details of the complexed ubiquitination that regulates cell death, and to clarify the molecular background of inflammatory bowel disease caused by its functional disruption, to create seeds for drug discovery and health maintenance.

Study of development of interventions for aged-related diseases and longevity based on understanding of proteostasis during aging

JOHMURA Yoshikazu
Professor, Division of Cancer and Senescence Biology, Cancer Research Institute, Kanazawa University

Senescent cells in living organisms originate from various cell types, and it is assumed that heterogeneous inducing mechanisms and functional diversity thereof differ greatly depending on the cell types contained in organs and tissues. Therefore, in this study, by performing omics analysis using mice capable of identifying, isolating, tracing, and genetically modifying at the single-cell level, the proteostasis dysfunction of senescent cells in individual aging and aging-related diseases would be investigated. Furthermore, the underlying mechanisms and regulatory factors behind them will be also extensively clarified.

Development of Innovative Therapeutics for Neurodegenerative Diseases Based on the Understanding of Lysosome Maintenance Mechanisms

SHIRAKAWA Ryutaro
Lecturer, Institute of Development,
Aging and Cancer, Tohoku University

The elimination of abnormal proteins by the autophagy-lysosome pathway is known to be important for the prevention of many diseases including neurodegenerative disorders. In this study, we aim to elucidate the molecular mechanism of autophagosome-lysosome membrane fusion by the atypical SNARE protein Ykt6, which undergoes a rare posttranslational modification with double prenyl groups, and to identify new therapeutic pathways for neurodegenerative diseases.

Comprehensive analysis of the slit diaphragm that plays a role in the clearance of proteins in body fluid

FUJITA Naonobu
Associate professor, Cell Biology Center,
Institute of Integrated Research, Institute of Science Tokyo

This study aims to elucidate the relationship between the clearance of body fluid proteins in the kidney and the pathogenesis of systemic amyloidosis. Using a high-throughput in vivo RNAi screening system, I will also uncover the mechanisms shaping the renal slit diaphragm, which plays a central role in the filtration of body fluids. This study would provide important clues for establishing new therapeutic strategies for chronic diseases; systemic amyloidosis and kidney diseases.

The regulation of amyloidostasis using the amyloid-selective Histidine oxygenation

HORI Yukiko
Associate Professor, Laboratory of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, The University of Tokyo

There is a strong need to establish disease-modifying therapies for neurodegenerative disorders, such as Alzheimer disease. Since these diseases are caused by amyloid deposition, the regulation of amyloidostasis in vivo is important as therapeutic strategy. We provide the amyloid-selective artificial oxygenation, which is our original technology using oxygenation catalyst to regulate amyloidostasis. In this study, to show the possibility of this technology as new therapeutics approach, we would like to reveal the mechanisms of amylodiostasis by oxygenation and develop the new oxygenation technology that is applicable for humans.

Regulation of proteostasis and disease development by Non-AUG translation initiation

MATSUMOTO Akinobu
Professor, Group of gene expression and regulation, Department of Biological Science, Graduate School of Science, Nagoya University

We have developed a new method named TISCA (Translation Initiation Site detection by translation Complex Analysis) to precisely identify initiation codons, and found that a large number of proteins are translated from Non-AUG initiation codons. Translation from the Non-AUG initiation codon significantly increases the complexity of the proteins. In this study, I aim to elucidate the mechanism of proteostasis regulation and diseases related to Non-AUG translation initiation.

Proteostasis through selective autophagy in vivo: from the molecular mechanisms to disease states

MORISHITA Hideaki
Professor, Department of Molecular Cell Biology, Graduate School of Medical Sciences, Kyushu University

In order for a living organism to develop normally and maintain homeostasis, a system that selectively degrades intracellular proteins and organelles should be essential. In this study, we will focus on "selective autophagy," a typical selective degradation system, and use zebrafish and mice to elucidate its role in various intracellular degradation phenomena in vivo, as well as the mechanism of cooperation with other degradation systems. Through this research, we aim to achieve a comprehensive understanding of various intracellular degradation mechanisms.

Disruption of Organelostasis and Vascular Disease

MORITO Daisuke
Associate Professor,
Showa University School of Medicine

Technological innovations such as imaging and mass spectrometry are changing the face of cell biology. Organelles, which were previously thought to be homogeneous and independent structures, actually have heterogeneous and complex structures, and seem to form a complex network. We will analyze the mechanism of organelle homeostasis and the vascular damage caused by its disruption.

RNA phase transition induces dysfunction of cellular proteostasis on prion-like proteins

YABUKI Yasushi
Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto University

G-quadruplex (G4) is one of DNA/RNA secondary structures which consist of G-rich sequences. We have recently demonstrated that G4RNA phase transition triggers to agglutinate prion-like proteins associated with a hereditary neurodegenerative disease. In the present study, we will elucidate a common mechanism underling dysfunction of cellular proteostasis on prion-like proteins by G4RNA phase transition in sporadic neurodegenerative disorders.

PRIME Started in 2022 ····· 3rd period

Regulation of inner nuclear membrane proteostasis

ARII Jun
Associate Professor, Center for Infectious Diseases, Graduate School of Medicine, Kobe University

A collapse of proteostasis in the membranous organelles can result in various diseases including hereditary disorders. Recently, the inner nuclear membrane (INM)-specific protein degradation systems have been reported, but their full details are unknown. The aim of this R&D program is elucidation of the INM-specific proteostasis regulation system and development of an innovative therapy that can help treat the diseases caused by abnormal protein accumulation at the INM.

Dissecting the mechanisms of phase separation formation and barrier homeostasis of epithelial tissues in stress response

ODA Yukako
Professor,
Graduate School of Biostudies, Kyoto University

In epithelial cells, the barrier function is carried by cell–cell adhesions called tight junctions (TJs). Regulation of TJ formation is important because disruption of TJs leads to inflammation and cancer progression. Recently, it has been reported that phase separation of ZO-1 promotes TJ formation. In this study, we will clarify the mechanism of ZO-1 phase separation to TJ formation and the role of TJ formation in the stress response of epithelial tissues.

Understanding the proteostasis linkage inside and outside the endoplasmic reticulum via co-translational degradation

KADOWAKI Hisae
Assistant Professor,Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Miyazaki

Protein quality is strictly regulated. Proteins that are not properly translated, folded, and transported are either repaired or degraded. When this protein quality control system is disrupted, the protein aggregation occurs, triggering a variety of diseases. This project aims to elucidate the molecular mechanisms by which proteins synthesized in the endoplasmic reticulum (ER), such as secretory proteins, are co-translationally degraded in the cytoplasm during ER stress, thereby maintaining proteostasis inside and outside the ER. Furthermore, I will attempt to develop novel molecular targets for the treatment of neurodegenerative diseases.

Single-cell covariation network analysis for proteostasis of metabolism-related proteins

KANO Fumi
Professor,
Institute of Innovative Research, Institute of Science Tokyo

By combining the cell image-based network analysis with the unique multiplex immunofluorescence method, we establish the novel single-cell covariation network analysis, that enables protein correlation analysis at the specific condition and time point. In this study, we focus on the proteostasis of metabolism-related proteins, and create a covariation network during neuronal differentiation of healthy or Alzheimer's disease patient-derived iPS cells. We will elucidate the regulatory mechanisms of how proteostasis of metabolic proteins respond to fluctuating intracellular environment by cell cycle, neuronal differentiation, and pathological conditions of Alzheimer's disease.

Study of synaptic proteostasis and its defects in neuronal disease

KISE Yoshiaki
Associate Professor,Graduate School of Science, The University of Tokyo

Neurons rely on the spatiotemporal protein quality control for their proper functions. Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are reportedly caused by the defects in the local proteostasis of the synaptic proteins. This study aims to reveal the mechanism of the synaptic proteostasis by structural biology using cryo-EM, thereby contributing to the development of the novel therapeutic strategies to cure neurodegenerative diseases.

Endothelial amyloid b precursor protein: posttranslational modification, proteostasis and clinical application

KITAZUME Shinobu
Professor,Clinical Laboratory Sciences, Fukushima Medical University

We have recently generated a new Alzheimer's disease (AD) model mouse, in which human amyloid b precursor protein (APP) is specifically expressed in the vascular endothelial cells. By crossing the mice with AD model mice, the resulting mice exhibited massive vascular amyloid deposition with age. In this research project, we focused on endothelial APP and elucidate the molecular mechanism by which the post-translational modification of APP is linked to the Aβ production pathway, and to clarify the in vivo fate of endothelial APP.

Function and mechanism of chaperone RNA maintaining proteostasis in the cell

KITAMURA Akira
Associate Professor, Faculty of Advanced Life Science, Division of Functional Life Sciences, Hokkaido University

Based on various challenges in the molecular and cellular biology field, we know well that protein-based molecular chaperones make a significant contribution to the maintenance of proteostasis. However, is it true that the molecules that play the role of molecular chaperones are limited to proteins? This question was our starting point. We are now elucidating how RNAs with molecular chaperone functions, i.e., chaperone RNAs, work dynamically on proteins in the cell.

Study on proteostasis control of polar-localized membrane proteins and related diseases

SEGAWA Katsumori
Professor,Medical Research Institute, Institute of Sciecne Tokyo

Bile acid transporters are polarly localized in epithelial cells, and their proteostasis is tightly regulated. Flippases are molecules that distribute membrane phospholipids asymmetrically, and their mutations disrupt the proteostasis of bile acid transporters, leading to progressive familial cholestasis (PFIC). This study aims to elucidate the molecular mechanism of membrane lipid-mediated proteostasis of bile acid transporters and the pathogenesis of PFIC.

Chronoproteostasis: Mechanisms and clinical approach for the circadian rhythm sleep disorder by dysfunction of protein proteostasis.

HIRANO Arisa
Assistant Professor,Faculty of Medicine/ WPI-IIIS, University of Tsukuba

Circadian clock is a fundamental biological system regulating many physiologies showing 24-hour rhythms, and disruption of circadian rhythms is known to induce various physical and mental disfunctions. The circadian molecular oscillation is tightly regulated by proteostasis of clock proteins (chronoproteostasis). In this study, we used circadian rhythms sleep disorders model mice and try to understand the mechanism and impact on physiology of the disorders caused by abnormal chronoproteostasis. We also aim to establish a method of medical intervention for the circadian rhythms sleep disorders.

Molecular basis of proteostasis in pancreatic β cell of pre-diabetes

MIYAKE Masato
Associate Professor, Institute of Advanced Medical Sciences, Tokushima University

Proteostasis in the endoplasmic reticulum is important for insulin production and secretion in pancreatic β cells to maintain glucose metabolism. Disruption of proteostasis by over-production of insulin to compensate for insulin resistance reduces its secretion, leading to the onset of type 2 diabetes. In this study, I aim to clarify the changes in proteostasis in pre-diabetes, especially focusing on translational regulation and molecular interactions. This project will contribute to the development of a therapy for type 2 diabetes by restoring pancreatic β-cell function.

(＊) indicates completed R&D projects.
Institution names, affiliations, and titles are as of the final year.