Stress

Elucidation of mechanisms for stress responses to disease development

Research and Development Objectives

Elucidation of stress responses and pathogenic mechanisms

Under “Stress” R&D area, the goal is to scientifically elucidate the biological responses at various different levels, from molecular/cellular levels to individual levels, caused by physical, chemical, biological, or emotional/psychological stress, and to develop an integrated understanding of stress responses and the mechanisms involved from the molecular/cellular level to the individual level.
We are surrounded by various different stressors, and new stressors have also emerged because of the changes in our lifestyles and social environments during the recent COVID-19 pandemic. Prevention of diseases triggered by such stressors is important to improve our QOL.
Specific goals of this R&D area include (1) elucidation of stress adaptation or avoidance systems in humans with a focus on applications in disease prevention, and elucidation of the mechanisms involved between the breakdown of these systems and disease onset; (2) identification of markers that allow objective evaluation of stress status in humans or prediction of disease onset due to stress, and elucidation of their pathophysiological significance; and (3) research and development of new techniques or methods, new measuring devices, or signal processing technologies that allow accurate, detailed, and long-term capture of human biological information that fluctuates subtly with exposure to stress.

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AMED-CREST Started in 2023 · 1st period

Integrative understanding of molecular stress and individual stress for discovering new stress pathologies through innovative AI development

OKAZAWA Hitoshi
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In this research, we will use AI to comprehensively understand the relationship of big data corresponding to molecular stress, cellular stress, and individual stress, and based on this, we will reversely predict the stress state of cells and molecules from biological information. Furthermore, by incorporating the newly developed AI technology, the ultimate goal is to develop technology that can estimate the ""molecular stress state"" of human brain cells live and in real time using biological information devices such as wearable electroencephalography.

Mechanostress-induced brain DNA damage and its life-course disease risk

KENGAKU Mineko
Professor,
Institute for Advanced Study, Kyoto University

Neurons in the brain have a limited capacity for replacement and accumulate DNA damage due to high oxidative stress and transcriptional activity. Excessive DNA damage is a primary trigger of neurodegeneration and dysfunction in disease and normal ageing brains. The principal investigator has discovered massive and transient DNA damage in newborn neurons by mechanostress during normal brain development. The primary goal of this study is to identify the mechanisms of the formation and repair of the mechanostress-induced DNA damage in developing and adult neurons, and to verify the disease risk of its genetic disruption or external disturbance.

Study of mechanisms of mental stress-induced cardiovascular pathogenesis using stress response control technology

NAKAMURA Kazuhiro
Professor,
Nagoya University Graduate School of Medicine

The mechanism by which mental stress affects organ functions and causes disease is unknown. In this study, we will conduct animal experiments using the stress response control technology we developed, and elucidate the mechanism by which mental stress causes cardiovascular diseases based on the animal experimental data and human clinical data. In addition, we will explore the central neural circuits underlying the neuroscientific entity of mental stress to present central targets to mitigate stress. Through this research project, we will contribute to the development of new technologies for prevention and treatment of stress-induced cardiovascular diseases.

Integrated understanding of mental frailty from non-neuronal stress engrams and its application to diagnostic treatment

MASUDA Takahiro
Professor, Medical Institute of Bioregulation,
Kyushu University

In this study, we will reveal early life stress-induced persistent cellular/molecular alterations in non-neuronal cells and brain-periphery cellular network transformation (we define them as "stress engram"). In addition, by getting to the bottom of the stress engram, we will comprehensively understand the molecular mechanisms of mental frailty that can lead to disease development, and ultimately try to establish the functional intervention techniques for the development of diagnostic treatments in humans and create an objective index and measurement technology for evaluating susceptibility and vulnerability to stress.

Molecular mechanisms of pathogenesis of stress-induced disease and development of stress biomarker detection technology

MURAKAMI Masaaki
Professor, Institute for Genetic Medicine,
Hokkaido University

Stress induces the onset and exacerbation of various chronic inflammatory diseases. However, since sensitivity and tolerance to stress vary with individual genetic and environmental predispositions, it has been difficult to promptly identify the danger signals in the body in response to stress, and prevent diseases. In this R&D, we will (1) identify specific stress-responsive factors and cells, (2) prove their causal relationships with pathogenesis, and (3) establish a fast and high sensitive quantum measurement system for them using samples from novel disease models, and human patients and health examination cohorts.

AMED-CREST Started in 2024 · 2nd period

Exploration of life environmental stress markers in the skin and their application in stratified medicine for atopic dermatitis.

KABASHIMA Kenji
Professor,
Kyoto University Graduate School of Medicine

The skin is exposed to various environmental stressors, which can disrupt skin homeostasis and contribute to the onset or worsening of atopic dermatitis. This study aims to scientifically and comprehensively elucidate the biological responses to different environmental stressors, from the cellular level to the whole organism. By identifying specific stress markers associated with each type of stressor, we seek to classify and stratify endotypes of atopic dermatitis patients. This approach could lead to more personalized and effective treatments based on the individual stress responses in atopic dermatitis patients.

Understanding the pathogenesis of diseases and disorders resulting from metabolic/social stress by uncovering the mechanism behind the therapeutic/preventative effects of exercise-mimicking mechanical intervention

SAWADA Yasuhiro
Director, National Rehabilitation Center for
Persons with Disabilities, Hospital

Through mechanical stimulation-based interventions in animal models and molecular/cellular experiments, we aim to replicate the anti-metabolic and anti-social stress effects of exercise. This approach seeks to elucidate the mechanical factors involved in the pathophysiology and etiology of diseases caused by these stresses. Furthermore, clinical trials will be conducted to achieve proof of concept for findings obtained from animal and cellular studies, leading to the development of effective treatments and preventive strategies.

Elucidation of molecular mechanism of neurodegenerative and neuromuscular diseases pathogenesis by disruption of lysosomal stress response and development of ultra-early biomarker

NAKAMURA Shuhei
Professor,
Faculty of Medicine, Nara Medical University

In many neurodegenerative and neuromuscular diseases such as Alzheimer's disease and Parkinson's disease, dysfunction of intracellular degradation organelle, lysosome is observed from very early stage. In this study, we consider the failure of the 'lysosomal stress response', a resilience mechanism against various stresses to lysosomes, as the main cause of the lysosomal dysfunction and will elucidate its molecular mechanism and pathological significance in neurodegenerative and neuromuscular diseases. Furthermore, we aim to develop biomarkers to detect the failure of the lysosomal stress response and to realize ultra-early diagnosis of neurodegenerative and neuromuscular diseases.

Study of the early molecular pathways and drug discovery of idiopathic pulmonary fibrosis caused by lung stem cell stress.

MORIMOTO Mitsuru
Team Leader,
RIKEN Biosystems and Dynamics Research Center

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive respiratory disease of unknown cause, and various stresses into lung cells are thought to be the staring point of IPF development. We have innovated pulmonary fibrosis organoids to analyze the pathogenesis of IPF at the cellular and molecular level. Using various in vivo stress models, live-vivo imaging, human pathology sample analysis, and organoid culture systems, we will investigate the mechanism of IPF pathogenesis, identify early IPF markers, and search for drug discovery seeds.

PRIME Started in 2023 ····· 1st period

Study of regulation of metabolic stress–induced cell death and chronic inflammation in the liver and adipose tissue

INABA Yuka
Associate Professor,
Institute for Frontier Science Initiative, Kanazawa University

Metabolic stress caused by overnutrition triggers chronic inflammation in the metabolic organs, resulting in non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus. Especially, chronic inflammation of the liver and adipose tissue interacts with each other, and plays a central role in these pathogenesis. In the development of chronic inflammation caused by metabolic stress, cell death plays an important role. This project aims to elucidate the regulatory mechanism of cell death by linking metabolic stress due to overnutrition with chronic inflammation of the liver and adipose tissue.

New genetic tools for spying on the stress-induced perturbation of hormone signaling

INO Daisuke
Lecturer,
Graduate School of Medicine Osaka University

The perturbation in hormonal levels has been proposed as a fundamental cause of the development of stress-induced disorders. Nevertheless, the direct observation of hormonal dynamics with precise spatiotemporal resolution has not been achieved. Furthermore, the causal relationship between dysregulated dynamics of stress-related hormones and disease onset remains elusive. Resolving these problems is of importance to bridge the gap between stress exposure and disease development. In this research, we aim to develop new tools to "visualize" and "manipulate" the signaling dynamics of stress-related hormones. We will also explore the application of these tools in experiments with animal models.

Molecular and circuit mechanisms responsible for behavioral changes induced by early-life stress

KAWAGUCHI Daichi
Associate Professor, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Early-life stress is known to increase the risk of psychiatric disorders later in life. However, the mechanisms that explain postnatal stress vulnerability are not fully understood. In this study, we aim to identify specific cells and molecules that react to stress during development and how alterations in neural networks throughout the brain, based on these cells and molecules, can impact behavior in the long term.

Unconventional modifications of organellar membrane lipids by protein conjugation and cellular stresses

SAKAMAKI Jun-ichi
Associate Professor,
Juntendo University Graduate School of Medicine

Intracellular organelles regulate various cellular processes including signal transduction and biochemical reactions and activate quality control mechanisms in response to cellular and organellar stresses. We have discovered an unconventional modification of membrane lipids; the ubiquitin protein is covalently conjugated to phospholipids in organellar membranes. This study aims to understand the role of unconventional modifications of membrane lipids by protein conjugation in the regulation of organellar function and stress response mechanisms.

DNA damage response by the RNA spatiotemporal regulation via membrane-less organelles

SHICHINO Yuichi
Research Scientist,
RIKEN Cluster for Pioneering Research

When DNA is damaged by genotoxic stress such as ultraviolet, cells repair DNA using the response pathways. Dysregulation of this system led to diseases including cancer. In this study, I will investigate the relationship between the regulation of gene expression required for DNA damage responses and the spatiotemporal regulation of mRNAs via membrane-less organelles called Processing bodies (P-bodies) and elucidate the detailed molecular mechanism and its importance in DNA damage sensitivity of cancer cells.

Elucidation of novel mechanism of cellular stress response by the identification of components of stress-responsive liquid-droplets

TAKAHASHI Hidehisa
Professor, Yokohama City University
Graduate School of Medical Science

Stress from the outside is transmitted to cells, where it promotes the expression of genes which is necessary for cells to respond to stress. In this study, I focus on the stress-responsive liquid droplets that function in gene expression in response to stress and clarify their components. Furthermore, I aim to elucidate the mechanism by which liquid droplet formation is disrupted by excessive stress, thereby elucidating one aspect of the pathogenesis of stress-induced diseases.

Study of novel therapeutic methods for inflammatory bowel disease through an integrated understanding of the brain-gut network

Toshiaki Teratani
Associate Professor,
Keio University, School of Medicine

While inflammatory bowel disease induces psychological stress, many studies have suggested that psychological stress is also deeply involved in inflammatory bowel disease symptoms. However, the molecular mechanisms of how perturbation of the gut-brain axis is involved in inflammatory disease pathology have not been elucidated. Therefore, this study aims to explain inflammatory bowel disease's pathogenesis and progression mechanisms, focusing on the gut-brain axis.

Investigating Crohn's disease pathogenesis focusing on Paneth cells

MATSUZAWA Yu
Associate Professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

Crohn's disease is a type of inflammatory bowel disease, and the disruption of Paneth cells in the small intestine is associated with the disease. In this study, we first examine the mechanism by which the accumulation of cellular stress induces Paneth cell death. Next, we focus on a T cell effector API5 which protects Paneth cells against cell death, and examine the mechanism by which API5 functions and investigate what kind of stressor affects the API5-secretion. Our goal is to utilize API5 as a new therapeutic target and a novel biomarker for Crohn's disease.

Sensing brain metabolic flux responding to various stresses using singlet hydrogen gas.

MATSUMOTO Shingo
Professor, Faculty of Information Science and Technology,
Hokkaido University

Various endogenous and exogenous stresses commonly induce cognitive impairment including decline in concentration and working memory. In this study, hyperpolarized 13C magnetic resonance imaging (MRI) using parahydrogen-induced polarization, which enhances the sensitivity of 13C MRI more than 10,000 times, can be used to visualize metabolic alterations in local brain regions. We aim to realize an individualized diagnostic imaging technique that estimates the risk of developing cognitive impairment under combination of different types of stresses from metabolic alterations in brain using hyperpolarized 13C-labele pyruvate and other metabolic tracers.

Development of a stretchable pulse oximeter for long-term and continuous measurement of blood pressure

YOKOTA Tomoyuki
Associate Professor,
School of Engineering, the University of Tokyo

I will develop a "stretchable pulse oximeter" that can accurately and long-term measure dynamic changes of biological signals in response to stress. Furthermore, I will utilize biological signals such as pulse wave and blood oxygen ratio that can be continuously measured using the pulse oximeter as biological alternatives data to estimate biomarkers such as blood pressure, for which continuous changes could not be measured. Then I will analyze them using AI algorithms to give them medical significance.

PRIME Started in 2024 ····· 2nd period

Development of ultra-compact biosensors for real-time multi-monitoring of stress markers

ADACHI Taiki
Postdoctoral Researcher, Graduate School of Agriculture,
Kyoto University

This project aims to develop electrochemical biosensors that can measure stress markers and their candidates in vivo over a long period. The sensors are based on "conductive enzymes" that can directly transfer electrons from/to electrode materials, and have the features of real-time, multiple, and ultra-compact. This technology is expected to contribute to the discovery of new biomarkers by improving the spatial and temporal resolution of data and to the prediction and mechanistic elucidation of disease onset by simultaneous measurement of multiple markers.

Elucidation and control of the neural circuit of emotional responses to stress: regulation of depressive-like state in non-human primates

AMEMORI Ken-ichi
Associate Professor,
Institute for Advanced Study, Kyoto University

Chronic stress can increase the risk of developing depression, particularly in individuals with certain vulnerabilities. In this study, we aim to identify the neural circuits that regulate stress responses related to conflict and motivation in the decision-making processes of non-human primates. Using chemogenetics and transcranial focused ultrasound, we will control these stress responses and elucidate the mechanisms by which the striatopallidum pathway controls conflict and motivation. This research will also explore the potential for new non-invasive therapeutics to modulate stress responses in non-human primates.

R&D of Treatments Targeting Disease-Associated Immune Cells for Psychiatric Disorder Symptoms and Learning Disabilities Induced by Prenatal and Developmental Complex Inflammatory Stress

OHTSUKI Gen
Program-specific Professor,
Kyoto University Graduate School of Medicine

Mental disorders are not caused by a single stressor but rather by the accumulation of multiple factors, which increases the risk. Specifically, infections during a mother's pregnancy and childhood trauma raise the risk of developmental disorders and schizophrenia in children. Animal studies have confirmed that the combination of these factors leads to more severe behavioral abnormalities. Our research aims to unravel this mechanism and contribute to the development of future treatments.

Regulation of tolerance to temperature stress via trace metal ions

KUHARA Atsushi
Professor, Institute for Integrative Neurobiology /
Faculty of Science and Engineering, Konan University

Various metal ions are known as essential trace elements involved in the biological stress response. Among them, iron and copper ions are associated with relatively recently discovered cell death pathways. However, much remains unknown about the molecular mechanisms and their physiological roles in stress responses. This study aims to establish a new experimental model of cell death induced by temperature stress and to develop molecular markers using an original experimental system focused on the cold stress tolerance of a small model organism.

Development of therapeutic strategies by elucidating energy regulation disorders caused by metabolic stress in adipose tissue

SAKAGUCHI Masaji
Assistant professor,
Faculty of Life Sciences, Kumamoto University

Obesity is a modern health issue. Metabolic stress from excess energy intake due to a high-fat diet and lack of exercise leads to insulin resistance in organs. This is exacerbated by the atrophy of brown fat, which, especially with age, plays a significant role in maintaining body temperature through energy expenditure. This research aims to elucidate the mechanisms behind energy regulation failure caused by metabolic stress and to develop new treatment methods through the reactivation of brown fat.

Elucidating the mechanism behind chronic inflammation and its expansion triggered by stress memory and visualization of stress sensing

SHIBATA Sayaka
Associate Professor,
Graduate School of Medicine, The University of Tokyo

The effects of stress on cells are not merely temporary; they can accumulate as "stress memory," influencing future cellular responses and characteristics. This accumulation of stress memory is accompanied by epigenomic reprogramming, leading to qualitative changes in cells that may contribute to the chronicity and spread of inflammation. This study aims to elucidate how stress memory alters cellular plasticity and influences disease progression, and to visualize the sensing of environmental factors associated with stress memory.

Pathophysiology and clinical application of disrupted energy homeostasis mechanism linking stress with organ fibrosis

SOHARA Eisei
Associate professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

It is emerging that disease and environmental stresses prevent AMPK, the master switch for energy homeostasis, from correctly sensing intracellular energy failure states, leading to disruption of the energy state of organs and fibrosis. However, the mechanism is unknown. In this study, we will unravel the energy sensing mechanism of AMPK and its failure in fibrotic diseases, focusing on linkage between disease/environmental stresses and fibrosis. Then, we will develop novel therapeutic strategies for organ fibrosis diseases such as chronic kidney disease.

Development of Nano-PALDI mass spectrometry imaging technology to reveal mental health conditions from a single hair

TAIRA Shu
Professor, Graduate School of Agricutural Sciences, Fukushima University

Evaluation of mental health and diagnosis of mental disorder such as mood disorder, depression and manic depression is difficult by just blood test and interview. Thus, new scientific evaluation method is needed. Hair has daily information through the capillary vessel. Nano-Particle Assisted Laser Desorption/Ionization (Nano-PALDI) imaging mass spectrometry (IMS) can visualize stress signal (biomarker) from lengthwise section of hair. In this research, we aim to found stress biomarker via omics analysis to understand stress mechanism and easily evaluate mental health condition to avoid that change to mental disorder using Nano-PALDI IMS.

Study of integrated information in the brain-body network against social stress

NAKAI Nobuhiro
Project Associate Professor,
Graduate School of Medicine, Kobe University

This study addresses the unresolved issue of how social stress affects the brain and autonomic nervous system, and the mechanisms behind individual differences in stress response. By using VR technology and multi-sensory monitoring, the study aims to measure the real-time brain and body activity of mice subjected to social stress to better understand their stress states. Additionally, optogenetics will be employed to manipulate the peripheral and central networks, with the goal of developing new therapeutic approaches to improve stress conditions.

Mechanism of neurodegeneration by intranuclear RNA sequestration stress

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

Aggregation of prion-like proteins induced by disrupted proteostasis can be a pathogenetic factor in neurodegenerative diseases. RNA G-quadruplex (G4RNA) is an important nucleic acid secondary structure, forming scaffolds for the aggregation of various prion-like protein and contributing to their pathogenic acquisition. In this research project, we aim to elucidate the molecular mechanism of neuronal cell death by G4RNA-causing the intranuclear RNA sequestration stress response and in turn to reveal the pathogenesis mechanism of neurodegenerative diseases.