Aging

Bridging the fundamental mechanism of aging and the effective treatment of age-related disease associated with impaired functional system

Research and Development Objectives

Elucidation of the mechanisms relating to changes in biological robustness associated with aging and control of age-related diseases

In the “ageing” research area, basic studies that aim at clarification of fundamental mechanisms underlying aging and researches that tackle age-related diseases by inhibiting the process that contribute to accelerating aging are encouraged to reduce the number of patients suffering from those diseases. The studies and researches follow the previous project on aging and bridge the fundamental molecular mechanism and clinical application. To facilitate understanding of aging,
researchers will use model organisms to investigate the genetic, cell biological and inter-tissue/organ regulation that determine aging. In addition to these challenges, environmental cues that regulate or affect the speed of aging are also examined.
Methods to control aging will also be developed. Following findings of new principles of aging and mechanisms involved in the impairment of robustness and resilience that intrinsically function against aging, the researchers will identify the biomarker of aging and find novel therapy against accelerated aging.

Program Supervisor (PS)

MOCHIZUKI Naoki

Director General, National Cerebral and Cardiovascular Center Research Institute

Program Officer (PO)

FUKAMIZU Akiyoshi

Professor, Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance (TARA), University of Tsukuba

Program Officer (PO)

YASUTOMO Koji

Professor, Graduate School of Medicine, Tokushima University

Advisor

AIBA Atsu
Professor,
Graduate School of Medicine, The University of Tokyo

IMAI Toshio
Professor,
Graduate School of Medicine,Kobe University

KATAGIRI Toyomasa
Director, National Institute of Biomedical Innovation,
National Institutes of Biomedical Innovation, Health and Nutrition.

SAYA Hideyuki
Professor/Director,
Fujita Cancer Center, Fujita Health University

TSUDA Makoto
Professor,
Department of Pharmaceutical Health Care and Sciences, Kyushu University

NISHINA Hiroshi
Professor/Director,
Medical Research Institute,
Institute of Science Tokyo

FUKAMI Kiyoko
Professor Emeritus,
Department of Medical Science,
Tokyo University of Pharmacy and Life Sciences

FUKAMI Maki
Deputy Director, Research Institute,
National Center for Child Health and Development.

MUKOYAMA Masashi
Director,
Omuta Tenryo Hospital

YONEDA Yoshihiro
Director,
The Research Foundation for Microbial Diseases of Osaka University

AMED-CREST Started in 2022 · 1st period

Elucidation and control of “aging-signal network” originating from the gut

IGAKI Tatsushi
Professor,Graduate School of Biostudies,
Kyoto University

To understand the fundamental aging mechanism, it is crucial to identify the cell population responsible for animal aging and how the biological network originating from the aging-responsible cells causes age-related alterations in the organism. In this study, we focus on the "aging-responsible cells" that appear in the Drosophila gut with aging, and aim to elucidate how they are generated and induce the systemic aging-signal network, as well as to establish a methodology for manipulating this aging network.

Elucidation of the stem cell-centric mechanisms of skin resilience, aging and the associated inter-organ frailty network

NISHIMURA Emi
Professor, The Institute of Medical Science,
The University of Tokyo

The skin forms a large barrier organ that protects us from various environmental factors that cause errors and damage to the genome as well as wounds and microorganisms. Tissue stem cells are responsible for its resilience yet decline with aging. In this project, we aims to identify the cells, signals, and molecules responsible for the processes by focusing on stem cell dynamics and fates and to elucidate the actual mechanisms of the inter-organ frailty network through systemic factors and cell-cell interactions leading to individual frailty. We will finally apply the knowledge to treat or prevent aging-related diseases.

Study on the elucidation and regulation of crosstalk between gut bacteria and senescent cells that causes age-related homeostatic disruption

HARA Eiji
Professor,Research Institute for Microbial Diseases,
Osaka University

In addition to genetic factors, various external factors are involved in the maintenance of health throughout the life stages. However, it is difficult to identify external factors that act slowly across life stages and have not been elucidated until now. In this study, we clarify such external factors by focusing on the relationship between the gut microbiota and cellular senescence. Through this research, we aim to identify molecular targets for detecting and preventing the age-related decline in biological functions and the risk of developing diseases.

Elucidation of the regulatory mechanisms of neuronal and glial cell senescence and its application to the development of diagnostic and therapeutic methods for Alzheimer’s disease.

MIZUTANI Kiyohito
Professor, Institute of Advanced Medical Sciences,
Tokushima University

In Alzheimer’s disease (AD), physiological aging causes neuronal degeneration and death. However, the regulatory mechanisms of neuronal aging are largely unexplored. In addition, the mechanisms of disruption of the interaction between glial cells and neurons in the onset and progression of AD are also not fully understood. This project aims to elucidate the regulatory mechanisms of neuronal and glial cell senescence and their disruption in the onset and progression of AD, leading to the development of early diagnosis and curative therapy for AD.

Study of support and promotion for aging research

MINAMI Yasuhiro
Professor,Graduate School of Medicine,
Kobe University

In aging research, analysis using aging mice and a wide variety of high-precision, state-of-the-art technologies play an important role. In this R&D project, we will establish a stable and low-cost supply system of aging mice for R&D projects in the field of aging research, and distribute them appropriately and timely. This project will also aim to provide the multifaceted, high-precision, cutting-edge technical support necessary for the promotion of aging research in each R&D project as a joint research project in principle, and to foster young researchers who will lead aging research.

AMED-CREST Started in 2023 · 2nd period

Elucidating the Mechanisms by which Mitochondrial Homeostasis Impacts the Hierarchy of Cellular Senescence, Organ Dysfunction, and Individual Aging Phenotypes

OIKE Yuichi
Professor, Graduate School of Medical Sciences,
Kumamoto University

Mitochondria have pleiotropic biological functions, and their dysfunction cause not only reduced energy production but also changes in various cellular functions and organ dysfunction. The details of how mitochondrial homeostasis mechanisms change with aging and how these changes contribute to aging and its-related diseases are largely unknown. In this project, we aim to elucidate the molecular mechanisms governing the relationship between mitochondrial homeostasis and aging, ultimately leading to the development of strategies to extend healthy lifespan through appropriate intervention in mitochondrial homeostasis mechanisms.

"Study of Age-Related Phosphoinositide Transformations and Mechanisms of Aging and Disease"

SASAKI Takehiro
Professor, Medical Research Institute,
Institute of Science Tokyo

Aging influences various biological processes, leading to a decline in physical functions and an increased risk of disease development. Similarly, phosphoinositides (PIPs), a family of membrane lipids, are involved in the regulation of diverse cellular functions and the pathogenesis of diseases. In this study, we aim to genetically elucidate the mechanisms of aging control by PIPs metabolizing enzymes, understand the profiles of aging-regulatory PIPs molecular species, and develop aging control methods through interventions in the PIPs metabolic system.

Development of anti-aging methods focusing on qualitative changes in skeletal muscle

TAKAHASHI Satoru
Professor, Transborder Medical Research Center, Institute of Medicine, University of Tsukuba

Skeletal muscle dysfunction is directly linked to a decline in quality of life and has a significant impact on cognitive and metabolic functions via neural activity and blood flow, as well as immune function, and is therefore well related to individual lifespan, prognosis of various diseases, and cognitive function. In this study, we will elucidate the relationship between skeletal muscle "quality" and individual aging, which has been elusive. The results of this research will lead to the development of methods to induce qualitative transformation of skeletal muscle, and the possibility of anti-aging methods targeting skeletal muscle quality will be explored.

Study of the mechanisms underlying organismal aging induced by loss of organ-specific endothelial cell heterogeneity

FUKUHARA Shigetomo
Professor, Institute of Advanced Medical Sciences, Nippon Medical School

The precise roles of blood vessels in organismal aging remain incompletely understood. While blood vessels are vital for sustaining life by transporting oxygen and nutrients to all cells throughout the body, recent research has unveiled that they are not just conduits for delivering blood but also acquire organ-specific functions to maintain homeostasis. In this study, we aim to explore how aging impacts the diverse organ-specific functions of endothelial cells and clarify their significance in organ and organismal aging. This research will help in developing strategies to prevent and treat endothelial cell aging and age-related diseases.

Physiology of extracellular disposal of the waste during aging, and the pathophysiology of age-related diseases caused by its disruption

MATSUI Hideaki
Professor,
Brain Research Institute, Niigata University

We study the relationship between the extracellular waste disposal system as a physiological mechanism of aging and the pathophysiology of diseases caused by its failure. Through the extra-cellular disposal of waste products, we will understand the commonalities and individual pathophysiology of aging and various aging-related diseases at the molecular and individual levels, thereby laying a major foundation for the prevention and treatment of aging-related diseases and for healthy longevity.

AMED-CREST Started in 2024 ····· 3rd period

Mechanism underlying iron-mediated induction of cellular and organismal aging and its manipulation

IWAI Kazuhiro
Executive Vice president/Professor,
Graduate School of Medicine, Kyoto University

Although contribution of iron to senescence has long been suggested, its detailed mechanism has not been clear. We have found that senescent cells are resistant to ferroptosis, an iron-induced cell death. However, to achieve the resistance, senescent cells safely store iron too excess, which leads to acquisition of senescence traits. We also found that a newly discovered molecule that is required for iron acquisition contributes to the development of senescence-related diseases. In this study, we challenge to elucidate the mechanisms by which iron accumulation induces cellular senescence and senescence-related diseases, and to develop methods to control senescence.

Investigation of mechanisms underlying age-related alterations by in vivo imaging and machine learning approaches

KIKUCHI Kazu
Director, National Cerebral and Cardiovascular Center Research Institute

No therapeutic approaches have been established that enable early treatment of aging-related diseases. This conundrum could be attributed to our limited understanding of how aging is initiated and propagated in an organism. In this study, we will perform longitudinal imaging of age-related alterations using an emerging model organism with life-long transparency in all organs. The imaging data will be analyzed using a machine-learning approach to reveal the earliest alteration that occurs during aging, and the underlying cell and molecular mechanisms will be identified using single-cell and spatial multi-omics analysis. The results of this study will help us develop a therapy for aging-related diseases.

Development of innovative diagnostic and therapeutic strategy based on an understanding of the fundamental principles of cellular senescence

TAKAHASHI Akiko
Chief, Division of Cellular Senescence, Cancer Institute, Japanese Foundation for Cancer Research

Cellular senescence is involved as one of the fundamental mechanisms of aging. However, senescent cells in the body are highly diverse, and there are many unknown aspects regarding their induction mechanisms and their resistance to cell death. Additionally, there is currently no universal markers and noninvasive detection methods of senescent cells in vivo. In this study, we aim to understand the diversity of senescent cells and identify biomarkers that can be detected in vivo, with the goal of developing diagnostic and therapeutic strategies for age-related diseases.

PRIME Started in 2022 1st period

Research and Development to Decode Age-Related Changing Cells

OKI Shinya
Professor,
Kumamoto University

This study will attempt to understand the effects of senescent cells on surrounding cells, and to analyze the "whole" transcriptome of non-membranous organelles that form during aging.

Mechanisms and pathophysiological significance of age-associated reprogramming of liver macrophages

SAKAI Mashito
Professor,Department of Biochemistry and Molecular Biology, Nippon Medical School

Chronic systemic inflammation is associated with an increased incidence of age-related diseases, such as metabolic and cardiovascular diseases and cancer. In addition, it has been postulated to play a critical role in regulating physiological aging. Liver macrophages are the largest population of tissue macrophages in vivo that increase in number with aging and secrete inflammatory cytokines to induce chronic inflammation. This study aims to clarify the mechanisms of age-associated reprogramming of liver macrophages and how macrophages of aged liver alter biological robustness to cause diseases.

Elucidating the stem cell aging process caused by glycosylation abnormalities

SADA Aiko
Professor,
Medical Institute of Bioregulation, Kyushu University

The presence of glycans determines the structure, stability, and localization of glycoproteins, and it plays a crucial role in physiological and pathological conditions, such as development, tumorigenesis, and inflammation. Glycans are also required for stem cell regulations by modulating cell-cell and cell-matrix interactions. Using lectin microarray, a platform for high-throughput glycome analysis, our previous study provided a comprehensive glycan profiling of mouse epidermal stem cells during skin aging. This study aims to reveal the glycan-dependent mechanisms of skin aging at the stem cell level, with implications for applications in regenerative therapy and future treatments of age-related disorders, including cancer.

Unraveling the pathogenesis of age-related diseases by targeting a metaboltie sensor for clinical applications

SEKIYA Motohiro
Associate Professor, University of Tsukuba, Faculty of Medicine, Department of Endocrinology and Metabolism

We identified a novel metabolic system orchestrated by a transcriptional cofactor with metabolite sensing capabilities. The system plays a critical role in the pathogenesis of obesity and therapeutically targetable. Metabolism has been known to be profoundly intertwined with ageing processes, and indeed our recent observations support an attractive and plausible idea that our metabolic system can be targeted to extend lifespan and healthspan as well. We will unravel basic mechanisms of ageing and advance the clinical translation from a unique metabolite-centered perspective.

Clarification of the impacts of oxidative stress on tumor initiation by a novel intra-tumoral H_2O_2 imaging technique

TAKAHASHI Nobuaki
Associate Professor,
The Hakubi Center, Kyoto University

Reactive oxygen species (ROS) has long been implicated to serve as a key factor that initiates age-related diseases. However, it remains poorly defined how ROS induce the pathogenesis and whether ROS really act as a critical mediator for the pathogenesis. This proposal aims to clarify the impacts of ROS on 'tumor initiation' using a tumor-targeted ROS probe that we have recently developed. I believe that the proposed study will offer a new avenue in oxidative-stress and aging researches.

Elucidation of the mechanism of memory decline associated with age-related disruption of proteostasis

Tonoki Ayako
Associate Professor, Chiba University,
Graduate School of Pharmaceutical Sciences,

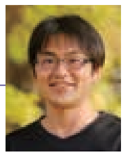
Age-related memory impairment such as dementia is caused by the accumulation of abnormal proteins in neurons and the disruption of neural circuits that support brain function. The proteostasis system degrades proteins within the cell, but its function declines with age. In this study, we aim to elucidate the mechanism by which age-related decline in the proteostasis mechanism disrupts neuronal functions and neural circuits, leading to a decline in memory.

Elucidating mechanisms of aging due to the disruption of NAD metabolism

NAKAGAWA Takashi
Professor,
Faculty of Medicine, University of Toyama

Nicotinamide adenine dinucleotide (NAD) is a co-enzyme and has attracted attention as one of the regulators of aging. However, the metabolic pathway of NAD in vivo is not fully understood, and its relationship with aging are remained unclear. In this research project, I will elucidate the spatiotemporal regulation of NAD metabolism in vivo and clarify how the disruption of NAD metabolism affects physiological aging and aging-related diseases. These results will lead to the development of future drug discovery and nutritional intervention for anti-aging.

Uncovering cell-cell communication within aged intestinal stem cell niche with a highly parallel analysis platform



HATTORI Kazuki
Project Assistant Professor,
RCAST, The University of Tokyo

The intestinal barrier deteriorates along with aging, which is a risk factor for aging-associated diseases. In this study, we will recapitulate the stem cell niche of the aged intestine by culturing the aged intestinal organoids and aged immune cells together in tiny wells or in micro-scale hydrogel units, which allows us to analyze cell-cell communication in a high-throughput manner. Leveraging this platform, we will identify the perturbation that re-activates aged stem cells and uncover the mechanisms of how the microenvironment contributes to stem cell aging.

Redefinition of aging as a function that optimizes longevity and physiology

MORI Masaki
Laboratory Chief,
National Center for Child Health and Development

How longevity is determined is a long-sought question that was cast on human beings, highly social animals. Why do human beings live long after losing fertility, while insects such as cicada and beetles die soon after mating? The existence of long-lived animals that keep much knowledge is profitable to society. Thus, persistent longevity after the loss of fertility is important and indispensable in terms of species conservation for human beings. From the viewpoint of "juvenility" and "juvenile gene program", we redefine the aging process as the system that maximizes longevity and values of aged animals to society.

Age-related changes in germline cells that cause chromosome translocations

YASUHARA Takaaki
Professor,
Graduate School of Biostudies, Kyoto University

The risk of infertility and chromosome aberrations in newborns increases with age. The increased risk is often explained by “aging”, however, what age-related changes in germline cells exactly cause the problem is not well understood. In this study, I aim to assess the tolerance of germline cells to transcriptional and nucleolar stresses that potentially induce chromosome translocations and elucidate how age-related changes affect that tolerance. Through this study, I will redefine the phenomenon previously vaguely referred to as "aging" in germline cells to explain what age-related changes actually cause chromosome aberrations in germline cells.

PRIME Started in 2023 ····· 2nd period

Dynamism of the immune cells in the cardiovascular tissues

UEDA Kazutaka
Assistant Professor,
The University of Tokyo

Most cardiovascular diseases are affected by aging. Recently, it has become clear that the adipose tissue surrounding blood vessels plays pathophysiological roles in the development of the diseases. This study aims to deeply understand the interactions among various cell types in blood vessels and their surrounding tissues through the latest spatiotemporal analysis, which leads to the development of therapies based on aging control for cardiovascular diseases.

Brain aging due to the decline of the nucleus-mediated novel regulatory system of neuronal activity

KUWAKO Ken-ichiro
Associate Professor,
Shimane University School of Medicine

Physiological brain aging is believed to be caused by a gradual decline in the activity of individual neurons and their plasticity, which results in the deterioration of neural functions. However, the mechanism of brain aging remains largely unknown, and no fundamental anti-aging strategy has been established. In this study, we will explore the mechanism of universal physiological brain aging based on the "new regulatory system of neural activity starting from the nucleus" and lead to the development of technologies to promote brain health and longevity.

Functions and mechanisms of nectin-1 in hypothalamic tanycytes for regulating individual

SHIMIZU Tatsuhiro
Assistant Professor,
Graduate School of Medicine, Kobe University

Feeding behavior closely relates to regulation of aging and longevity as dietary restriction prolongs lifespan of organisms. Hypothalamic tanycytes not only sense glucose concentration to control feeding behavior but also function as neural stem cell in adults. Much of the regulatory mechanism, however, remains unexplained. In this study, we will focus on nectin-1, a cell adhesion molecule, which is expressed in tanycytes, to elucidate its function and mechanism of action in individual aging.

Elucidation of the regulatory mechanisms of hematopoietic stem cell aging that causes chronic inflammatory diseases

TADOKORO Yuko
Assistant Professor,
Cancer Research Institute, Kanazawa University

Aging is characterized by a low-grade chronic inflammation. To understand the aging process, it is crucial to elucidate the fundamental mechanisms of age-associated systemic chronic inflammation, which is caused by hematopoietic stem cell (HSC) aging. However, it is unclear how this “HSC aging” occurs. In this study, we aim to elucidate the molecular mechanisms of HSC aging progression. Based on these findings, we also aim to develop approaches to suppressing the progression of age-related chronic inflammatory diseases by regulating HSC aging.

Elucidation of senescence-associated antigen-expressing cells that induce autoimmune response, and the mechanism underlying their pathological changes.

TSUKAMOTO Hirotake
Tenure-Track Associate Professor,
Center for Cancer Immunotherapy and Immunobiology,
Graduate School of Medicine, Kyoto University

While diverse types and traits of senescent cells make it difficult to predict susceptibility to disease and risk of frailty in aged individuals, they would be promising targets for the development of therapeutic strategies. In this study, we aim to clarify the differences in senescent cells that accumulate or are eliminated during the aging process through evaluating age-associated self-antigens that are targets of immune cells. Our results should lead to finding the targets for objective evaluation of aging status and "positive" and "negative" aspects of cellular senescence.

Analyses of Age-Related Transformation of Logistics through Vascular System with in toto Imaging Analyses

NAKAJIMA Hiroyuki
Section Chief,
National Cerebral and Cardiovascular Center Research Institute

Blood and lymphatic vessels are central tissues responsible for logistics in the body. Such vascular logistics are essential for the maintenance of biological homeostasis. Age-related deterioration of vascular function is implicated in major aging-related diseases. This research aims to understand aging as an age-related alteration of vascular logistics. Here, in toto live imaging analysis will be performed using multimodal reporter fish that capture age-related changes in vascular logistics as well as aging of blood vessels and tissues. This research is expected to provide an essential understanding of aging and elucidate therapeutic targets for age-related diseases by targeting vascular logistics.

Elucidation of the cellular senescence mechanisms of myofibroblasts involved in the exacerbation of age-related chronic inflammatory diseases and its therapeutic application

NAKAYA Michio
Professor,
Research Institute of Environmental Medicine, Nagoya University

Fibrosis is a condition characterized by the excessive accumulation of extracellular matrices, such as collagen, within tissues. It is observed in tissues afflicted with a multitude of age-related chronic inflammatory diseases. Myofibroblasts, responsible for the synthesis of collagen and various extracellular matrices, orchestrate the process of fibrosis. Their cellular senescence leads to the exacerbation of numerous age-related chronic inflammatory conditions. Consequently, in this study, we will analyze the cellular senescence mechanism of myofibroblasts and aim to develop new treatments for age-related chronic inflammatory diseases that target this mechanism.

Elucidating the immunosenescence mechanism associated with the decreased plasticity of resident memory T cells.

WATANABE Rei
Professor,
Graduate School of Medicine, Juntendo University

Many peripheral tissues embrace a sessile memory T cell fraction called resident memory T cells (TRM). TRM exhibit a strong response to antigens, acting as "guardians of the tissue." At the same time, they exert plasticity through activation, transitioning from sessile to circulating memory T cells, functioning as a "reservoir of systemic immunological memory." This study aims to investigate the potential link between decreased plasticity of skin TRM and immunosenescence, and explore strategies to counteract immunosenescence.

Age-dependent changes in brain-specialized endothelial lipid metabolism as a trigger of cerebrovascular dysfunction

YANAGIDA Keisuke
Senior Research Fellow,
National Center for Global Health and Medicine

Brain vasculature has unique properties to manage both high energy demand of neurons and their defense from harmful substances. Of note, aging is associated with a decline of these brain-specialized vascular functions, which underlies the risk of dementia. However, the molecular mechanisms underlying age-dependent cerebrovascular dysfunction is still unclear. In this study, we will reveal the age-dependent changes in brain-specialized endothelial lipid metabolism. Moreover, we will assess the possibility that the lipid changes would be a direct trigger of cerebrovascular dysfunction and dementia.

Study of the biological mechanisms of aging through multi-omics analysis of normal cells using single cell-derived models

YOSHIDA Kenichi
Chief,
National Cancer Center Research Institute

Accumulation of somatic mutations in normal cells caused by intrinsic and environmental factors has been implicated in the development of age-related disease such as cancers. Somatic mutations itself has also been associated with aging. In this study, we will grow single cell-derived organoids or colonies from normal cells derived from healthy donors and patients with premature aging syndromes, and perform multi-omics analysis, including whole-genome sequencing, to reveal the mechanism of normal and premature aging.

PRIME Started in 2024 ····· 3rd period

Study on the development of mitochondria-targeted treatment for aging in the hematopoietic system

NAKAMURA-ISHIZU Ayako
Professor, Tokyo Women's Medical University, Department of Microanatomy and Developmental Biology

Organismal aging maybe complicated by disruption of hematopoiesis and loss of functional hematopoietic stem cells which associates with the occurance of various age-related diseases. This study aims to investiagte the change in mitochondrial function, especially that of mitochondrial iron and mitochondrial dynamics, in aged hematopoietic stem cells. We wish to develop novel mitochondria-targeted strategies to manipulate hematopoietic stem cell fate.

Study of elucidation and overcome the mechanism of neuro-aging caused by abnormal protein accumulation and lysosomal dyshomeostasis

KAKUDA Keita
Assistant Professor,
Graduate School of Medicine, Osaka University

The brain is an organ that continues to decrease in the number of cells with aging. A pathological condition where abnormal protein accumulation accelerates aging is called a neurodegenerative disease. Developing treatments for such diseases requires understanding and overcoming the principles of neuronal aging. In neuronal aging, the damage to lysosomes, which are responsible for intracellular degradation, and the decline in damage response—referred to as lysosomal aging—are crucial factors. This study aims to elucidate the mechanisms of lysosomal damage response to abnormal protein accumulation in neuronal aging and contribute to the development of therapies.

Deciphering mitophagy as an anti-ageing programme

KATAURA Tetsushi
Assistant Professor,
Institute of Medicine, University of Tsukuba

Mitophagy eliminates dysfunctional mitochondria via autophagic degradation. We recently identified that mitophagy is necessary to suppress cellular aging, though the mechanism is yet to be defined. In this study, we will discover key factors responsible for cellular aging by investigating the target molecules of mitophagy. By using our unique small-molecule mitophagy activators, we will demonstrate that reactivating mitophagy can combat cellular aging, with the goal of establishing a new intervention strategy to promote healthy aging.

Functional restoration of Aged Hematopoietic Stem Cells Targeting the Program of Metabolic Plasticity

KOBAYASHI Hiroshi
Associate Professor,
Tohoku University Graduate School of Medicine

Hematopoietic stem cells are responsible for lifelong blood production, but with aging, the number of stem cells with reduced blood production capacity increases. It has been found that aged hematopoietic stem cells have higher metabolic plasticity compared to young hematopoietic stem cells, but the molecular mechanisms underlying this remain unclear. In this study, we aim to establish a machine learning model that integrates transcriptional information with metabolic analysis, including single-cell analysis, to predict the responsible genes. Comprehensive functional analysis will be conducted with the goal of restoring the functionality of aged stem cells.

Analysis of the functional roles of PNPO-PLP axis in age-related diseases

SEKINE Hiroki
Associate Professor,
Tohoku University Graduate School of Medicine

Chronic tissue hypoxia is associated with the pathogenesis of age-related diseases, but its molecular basis remains unclear. We have recently shown that chronic hypoxia leads to a decrease in pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, leading to the phenotypes associated with chronic hypoxia. This study aims to elucidate the impact of tissue hypoxia on age-related diseases by examining PLP dynamics, ultimately contributing to the development of new diagnostic and therapeutic approaches for these diseases.

Alteration of microglial characteristics regulated by micronuclear propagation and its impacts on aged cerebral blood vessels

TSURUTA Fuminori
Assistant Professor, Institute of Life and Environmental Sciences, University of Tsukuba

Microglia, the immune cells in the central nervous system, are known to undergo characteristic changes with aging and to regulate the functions of cerebral blood vessels. However, the precise mechanisms and physiological significance of these microglial transformations remain insufficiently understood. In this study, we aim to determine whether microglial changes induced by micronuclear propagation are involved in regulating the functions of aging cerebral vessels and in removing waste products. We will employ a comprehensive range of approaches, from molecular biology analyses to in vivo imaging in mice, to address these fundamental questions.

Study of the proteasome dynamics along aging and its application to aging control

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

Recent findings have revealed that functional alterations in the proteasome, the key machinery for intracellular protein degradation, are implicated in the onset of numerous pathologies, including aging, neurodegenerative disorders, and inflammatory diseases. However, a comprehensive understanding of the regulatory mechanisms of the proteasome dynamics and their connection to aging remains elusive. This study aims to modulate aging and related pathologies by elucidating novel proteasome control mechanisms and applying these insights to develop targeted interventions.

Elucidating aging mechanism associated with clonal hematopoiesis originating from kidney DNA damage

HAYASHI Kaori
Professor,
Keio University School of Medicine

Recently it has shown that chronic kidney disease is a major factor that accelerates systemic aging; however, the reasons for the strong involvement of the kidneys remain unclear. This study aims to investigate the possibility that DNA damage in the kidneys may contribute to systemic aging through hematopoietic stem cell aging, such as clonal hematopoiesis, leading to development of new therapeutic strategies for age-related diseases.

Study of specialized ribosomes and impaired nucleolar dynamics during cellular senescence

YOSHIKAWA Harunori
Assistant Professor, Fujii Memorial Institute of Medical Sciences,
Institute of Advanced Medical Sciences, Tokushima University

Senescent cells increase in the translation particularly of specific proteins promoting senescence e.g. SASP factors. Senescent cells also exhibit morphological changes in nucleoli where ribosome biogenesis occurs. Using my unique techniques to analyze the ribosomes and nucleolar pre-ribosomal particles by size exclusion chromatography together with mass spectrometry-based proteomic analysis, I aim to elucidate how altered ribosome biogenesis in the nucleoli and specialized ribosomes and their roles in the translation contribute to cellular senescence. This project will lead to the development of new tools to identify the senescent cells.

Elucidating the Mechanisms of Osteocyte senescence and Its Pathophysiological Significance Through a Mechanobiology Approach

YOSHIMOTO Tetsuya
Assistant Professor, Dept. of Innovation and Precision Dentistry,
Hiroshima University Hospital

Appropriate mechanical stress, such as exercise, is effective in preventing musculoskeletal disorders in middle-aged and older adults. However, the systems and mechanisms by which mechanical stress improves bone quality and counteracts aging remain poorly understood. In this study, we will focus on osteocytes, which are central to bone metabolism and act as important mechanosensors, aiming to elucidate the molecular mechanisms by which mechanical stress regulates osteocyte aging, thereby contributing to the prevention and treatment of age-related bone metabolism disorders.