Title of Project：Homeostatic Regulation by Various Types of Cell Death

Masato Tanaka
(Tokyo University of Pharmacy and Life Sciences,
School of Life Sciences, Professor)

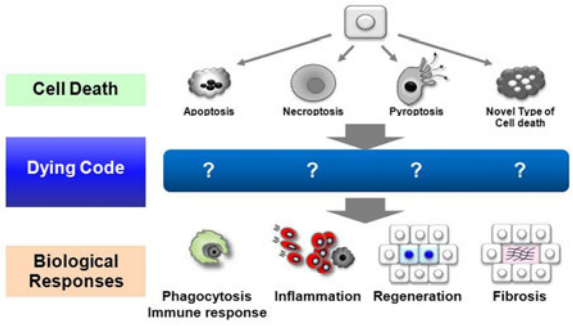
Research Project Number：26110001　Researcher Number：00294059

【Purpose of the Research Project】

Senescent cells, virus-infected cells, and cancer cells are eliminated by cell death. It is well recognized that cell death is the terminal step in the lives of cells, and that dead cells should be swiftly removed. Recently, however, it appears that dead cells are the source of signals that initiate several biological responses, including immune reaction, inflammation, repair, regeneration, and fibrosis.

Most cells possess several programs for cell death. In metazoan physiology and pathology, different types of cell death are thought to take place simultaneously and complementarily. Therefore, it is very important to uncover the biological cascades initiated by each type of cell death, and to integrate those findings to better understand biological phenomena associated with cell death.

In this project, we focus on signals derived from dead cells, and attempt to reveal how those signals contribute to regulating biological responses, thereby creating a new paradigm, “dead cells as signaling cells.”



“Dying Code” Regulates Various Biological Responses

【Content of the Research Project】

We will analyze the molecular mechanisms of cell death and the biological responses initiated by it, with the aim of elucidating the physiological and pathological roles played by each type of cell death. Specifically:

1. We will attempt to reveal the molecular mechanisms underlying each type of cell death, and elucidate the physiological and pathological conditions involved by developing detection methods and in vivo imaging techniques.

2. We intend to identify signaling molecules derived from dead cells, and reveal the biological responses induced by those molecules in dead cell removal, immune reaction, inflammation, repair, and regeneration.

In addition to the individual projects of each member of our research group, collaborative research projects will be conducted by all members. In the collaborative research projects, researchers from different fields of expertise will analyze a tissue-injured model, and integrate their findings in an effort to thoroughly understand the underlying mechanisms of the biological responses to the tissue injury, by developing a new concept, “not only cell death itself but also its signals regulate biological responses.”

【Expected Research Achievements and Scientific Significance】

As a variety of biological responses associated with tissue injury, including immune reaction, inflammation, repair, and regeneration, are initiated by cell death to promote the biological cascade, this innovative research area will further clarify the roles of signals derived from dead cells, and provide us with a common principle of the biological responses. Furthermore, as this common principle is assumed to be deeply involved in the pathology of various diseases, this research project is also expected to provide therapeutic targets and candidates for biomarkers of several diseases in the future.

【Key Words】

Nowadays, the programmed cell death includes not only apoptosis, but also non-apoptotic cell death, such as necroptosis and pyroptosis.

【Term of Project】 FY2014-2018

【Budget Allocation】 953,900 Thousand Yen

【Homepage Address and Other Contact Information】

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Title of Project : Oxygen biology: a new criterion for integrated understanding of life

Yasuo Mori
(Kyoto University, Hall of Global Environmental Studies, Professor)

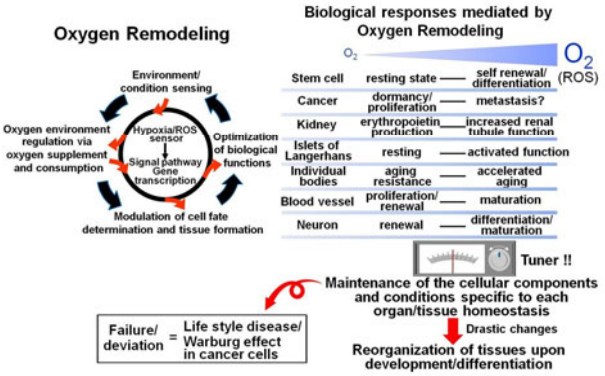
Research Project Number : 26111001 Researcher Number : 80212265

【Purpose of the Research Project】

Molecular oxygen (O_2) is indispensable for aerobic organisms. From the perspective beyond the classical understanding of O_2, a new biology field "oxygen biology" is emerging.

The first novel point of view in oxygen biology is the significance of the different levels of hypoxia inside the bodies. It is known that O_2 supply is increased under hypoxic conditions to prevent damages. However, recent studies show that the internal hypoxic environment has physiological significance, overturning the preconceptions of O_2. The second point is the role of O_2 and reactive oxygen species (ROS) and electrophiles as signaling molecules. New O_2-originating species have been identified, but their biological insights are still limited and not investigated for systems as a whole within a specific internal O_2 environment.

Based on our unprecedented concept "oxygen remodeling" that cells actively regulate O_2 concentration to the optimal range according to their needs, this project will aim to unveil how cells sense, respond and utilize the O_2 environment, by focusing on energy metabolism and ROS signaling.



Nobel concept of oxygen biology: "Oxygen Remodeling"

【Content of the Research Project】

This research project will be coordinated and conducted based on the specific aims A01-A03.

A01 aims to clarify the mechanisms by which hypoxic environments *in vivo* are detected and formed from the perspective of energy metabolism. Specifically, hypoxia effectors such as Hypoxia-inducible factors regulated by prolyl hydroxylases/unknown hydroxylases will be identified, to reveal the acute and chronic regulatory systems in the cells and tissues.

A02 studies the mechanism of how ROS, reactive nitrogen/sulfur species (RNS/RSS) mediate and confer reversibility to elementary processes in the signaling pathways evoked by O_2, to elucidate active utilization of hypoxic environments in oxygen remodeling for the optimization of functions of tissues and cells.

A03 will develop novel *in vivo* imaging techniques to visualize hypoxia and electrophilic reactive species, to secure the methodological basis to conduct A01 and A02.

【Expected Research Achievements and Scientific Significance】

The new field "oxygen biology" established by the fusion of leading-edge researches will bring forth world-leading achievements. Also, this project will integrate and restructure different research fields to significantly improve the overall levels of academia. Furthermore, scientists from various generations gathering at the common platform of oxygen biology will facilitate cultivation of the next generation.

This project will help to prevent and develop treatments of lifestyle-related diseases, cancer, aging, inflammation, caused by the deviation of O_2 and ROS signals. These developments will contribute to solving critical social problems in super-aging society and adaptation of our life to the changes of global environment.

【Key Words】

Oxygen remodeling: the concept that the cells actively control O_2 concentration to be in the optimal range according to their needs.

【Term of Project】 FY2014-2018

【Budget Allocation】 1,176,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.oxygenbiology.net/
mori@sbchem.kyoto-u.ac.jp

Title of Project : Mechanisms underlying the functional shift of brain neural circuitry for behavioral adaptation

Kazuto Kobayashi
(Fukushima Medical University, School of Medicine, Professor)

Research Project Number : 26112001　Researcher Number : 90211903

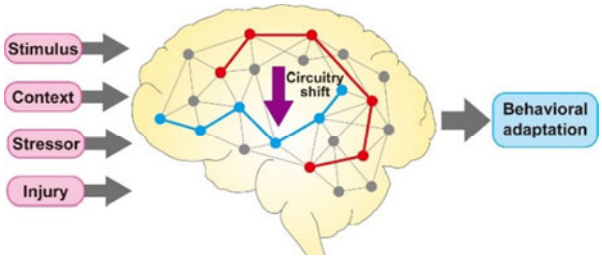
【Purpose of the Research Project】

Our brain functions are based on the network in which a number of neurons are connected (neural circuitry). The neural circuitry is known to undergo dynamic transition during the development and learning processes. For instance, the circuitry that mediates the acquisition of operant conditioning in which animals learn the behaviors through trials and errors is different from one that mediates execution of habitual behaviors. In addition, when the injury of the brain or spinal cord impairs motor functions, the neural circuitry in the brain is reorganized at a large scale during the training and rehabilitation.

The "functional shift" including the transition and rearrangement of neural circuitry is an important process for animals to adapt flexibly their behaviors to environmental changes and to recover the impaired functions. The mechanism on why and how the functional shift occurs has been poorly investigated. In this project, we use new technologies to manipulate and analyze the neural circuitry and aim to elucidate the mechanism underlying the development and transition of neural circuitry related to behavioral adaptation and the rearrangement of the circuitry following the brain and spinal cord injury.

【Content of the Research Project】

To understand the mechanism of the functional shift of the neural circuitry underlying the behaviors, it is important to manipulate the function of specific neuronal types and pathways that constitute the circuitry (circuitry manipulation) and to observe the resultant changes in the activity of brain regions and behaviors. Through this approach, we can clarify the causal relationship between the circuit structure and function.



Here we apply our new strategy to manipulate specific neural types and pathways, and combine the results with the functional imaging and large-scale computational modeling to characterize dynamic changes of the neural circuitry. By analyzing these changes leading to the behaviors, we study how the neural circuitry operates and shifts during the learning processes and behavioral switching. Furthermore, we try to understand the mechanism on how the neural circuitry is reorganized and achieves the recovery, when the brain or spinal cord is injured.

【Expected Research Achievements and Scientific Significance】

Dysfunction of the neural circuitry is related to the pathogenesis of neuropsychiatric and neurological diseases. The results obtained from the study of the circuitry shift will provide not only the academic information but also the significance in clinical science. The results lead to an understanding of the circuitry mechanism of the impairments of higher brain functions and the compensation after the neural injury. The detailed analysis of circuitry dynamics is expected to develop therapeutic and rehabilitative approaches based on scientific evidence to improve pathology of the diseases.

【Key Words】

Neural circuitry: A neuronal cell is composed of a cell body, dendrite, and axonal structure, and the axonal terminals make a synapse with other neuronal cells. Neurotransmitters are released from synaptic terminals and convey signals to another cell. Circuitry manipulation: Genetic manipulation technology provides the strategy to induce neuronal ablation and inhibit synaptic transmission. In addition, the technology enables us to control specific neuronal activity by optic stimulation and chemical substances.

【Term of Project】

FY2014-2018

【Budget Allocation】

1,213,600 Thousand Yen

【Homepage Address and Contact Information】

URL: http://fmu.ac.jp/netshift/
E-mail: netshift@fmu.ac.jp

Title of Project : Non-coding RNA neo-taxonomy

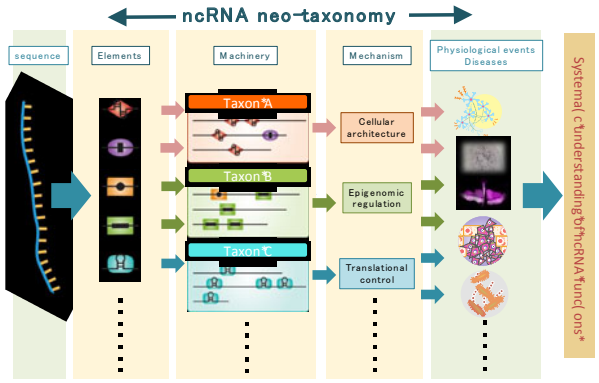
Tetsuro Hirose
(Hokkaido University, Institute for Genetic Medicine, Professor)

Research Project Number : 26113001 Researcher Number : 30273220

【Purpose of the Research Project】

Recent transcriptome analyses have revealed that large portions of the mammalian genomes produce numerous numbers of non-coding RNAs (ncRNAs), which play important regulatory roles in various biological events. Just like proteins, ncRNAs are extremely diverse and are considered to possess their own characteristics that determine their specific functions. However, ncRNAs have so far been collectively defined as the RNAs that are unlikely to code polypeptides, in a manner unlinked to their own features. To accelerate our understanding of ncRNAs, this research project aims to systematically characterize and classify the features of individual ncRNAs, toward our ultimate goal to establish a new system of ncRNA categorization termed "non-coding RNA neo-taxonomy."

The concept of ncRNA neo-taxonomy



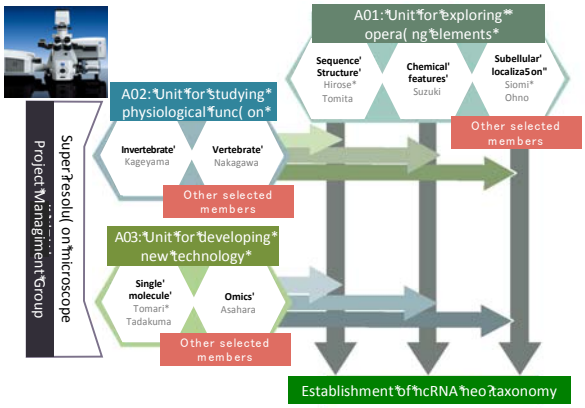
【Content of the Research Project】

In this research project, the fundamental functional units of ncRNAs are termed "operating elements" and the ribonucleoprotein complexes formed on the operating elements are termed "operating machineries". The research project team is comprised of the following three units in order to conduct systematic identification of operating elements and to link them to operating machineries and physiological functions.

A01: Unit for exploring operating elements
A02: Unit for studying physiological functions
A03: Unit for developing new technologies

In addition, the project management group will set up a super-resolution microscope as a common facility to promote investigation of intracellular localization of operating machineries. Through the collaborative works of the three research units and the research management group, this project aims to establish "non-coding RNA neo-taxonomy" for systematic understanding of ncRNA functions.

Organization of the research project



【Expected Research Achievements and Scientific Significance】

Establishment of "non-coding RNA neo-taxonomy" will make it possible to predict the functions of unannotated ncRNAs based on their operating elements. This will greatly facilitate the systematic understanding of ncRNA functions and will pave the way for controlling biological phenomena, e.g., artificial designs of functional ncRNAs and chemical screening systems that target ncRNAs. The expected research accomplishments will provide critical insights into ncRNAs for better understanding of RNA toxicity diseases such as neurodegenerative disorders and for developing new pharmaceutical targets.

【Key Words】

Non-coding RNAs: RNAs that do not code polypeptides but play various regulatory functions.

【Term of Project】 FY2014-2018

【Budget Allocation】 1,129,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://ncrna.jp

Title of Project : Cell competition: a mechanism for survival of the fittest in the multi-cellular community

Yasuyuki Fujita
(Hokkaido University, Institute for Genetic Medicine, Professor)

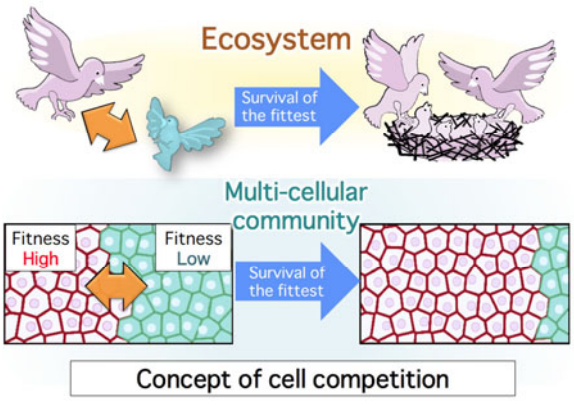
Research Project Number : 26114001　Researcher Number : 50580974

【Purpose of the Research Project】

In an ecosystem, a variety of biological individuals compete with each other for the limited space, food and spouses. Consequently, the fittest will survive, a process known as 'the survival of the fittest'. Recent studies have revealed that comparable phenomenon also occurs in a multi-cellular community; the identical type of cells with different properties competes with each other for survival, a phenomenon named as '**cell competition**'. It has become clear that cell competition is involved in various processes such as embryonic development, selection of the fittest stem cells, and elimination of precancerous cells. However, the molecular mechanisms underlying these processes still remain largely unknown. Furthermore, it is highly plausible that cell competition is involved in a number of yet unidentified physiological and pathological processes.

Here, we will be establishing a comprehensive and integrated research body focusing on cell competition. The main objectives are as follows;

1) To understand the full picture of the molecular mechanisms governing cell competition.
2) To elucidate how cell competition is involved in the establishment and maintenance of multicellular communities.
3) To reveal whether and how the derailment of cell competition leads to pathological conditions or diseases.



Concept of cell competition

【Content of the Research Project】

To reach at the goals described above, we will investigate the following research topics.

1) Elucidation of the molecular mechanisms regulating cell competition
2) Establishment and analyses of *in vivo* model systems for cell competition
3) Mathematical analysis on cell competition

We will share the outputs obtained from all research teams and will comprehensively and cooperatively develop collaborations within the whole group. Furthermore, to intensify and potentiate the productivity, we will additionally recruit research groups studying cell competition from a variety of angles; e.g. clinical medicine, innovative imaging techniques, mathematics, biophysics. Hence, we aim to uncover the full picture of cell competition.

【Expected Research Achievements and Scientific Significance】

The molecules specifically functioning or accumulating during cell competition can be used as biomarkers to capture the occurrence of cell competition, leading to identification of physiological or pathological processes that involve this phenomenon. Hence, the development of this research area would substantially influence various research fields including cell biology, developmental biology, physiology, oncology and clinical medicine.

【Key Words】

Cell competition: competition between the identical type of cells with different properties (e.g. cell proliferation, cell polarity, oncogenic mutations)

【Term of Project】 FY2014-2018
【Budget Allocation】 1,215,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://cell-competition.com
yasu@igm.hokudai.ac.jp

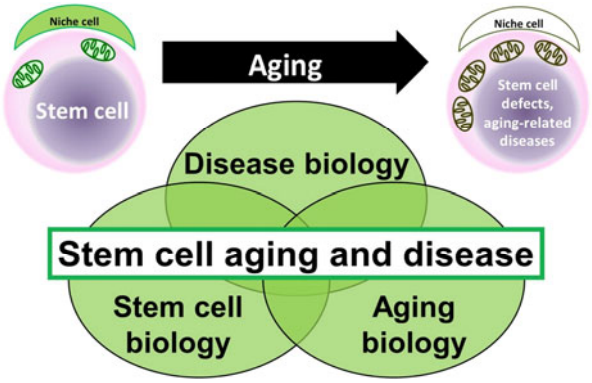
Title of Project：Establishing a new paradigm of pathogenesis of the diseases through the understanding of stem cell aging

Atsushi Iwama
(Chiba University, Graduate School of Medicine, Professor)

Research Project Number：26115001　Researcher Number：70244126

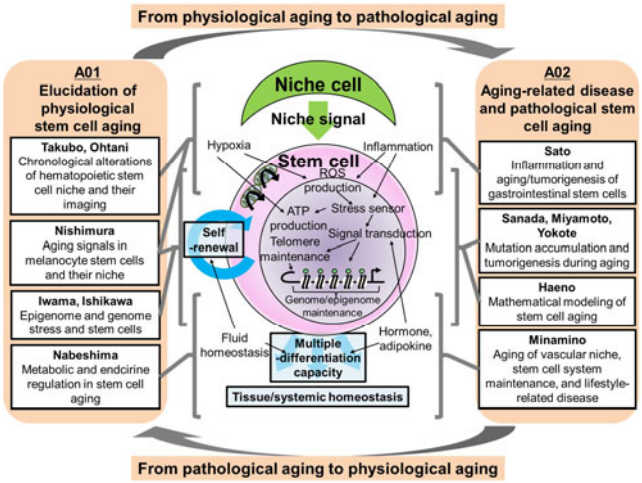
【Purpose of the Research Project】

Physiological changes of tissues with age are closely associated with aging-related diseases. Given that aging-related diseases are increasing rapidly in this super-aged society, a scientific approach that targets aging-related diseases is required to achieve health and long life. Recent advances in stem cell research have demonstrated clearly that the continuous regenerative process governed by the stem cell system maintains tissue homeostasis. In the meantime, stem cells, which had been thought to be ageless, appeared to have limited life, and physiological as well as pathological aging of stem cells and their niches, namely "Stem Cell Aging" largely accounts for aging-related diseases. In this research area, we will challenge one of the latest topics, "Aging and diseases" from the viewpoint of "Stem Cell Aging". We will recruit researchers from various related research areas and, through collaborative research, generate a new paradigm of the pathogenesis of aging-related diseases.



【Content of the Research Project】

With a hypothesis that aging-related diseases occur due to failure in various anti-aging systems that operate in stem cells and their niches, we will decipher the mechanisms of physiological and pathological aging (aging-related diseases) through understanding the impact of "Stem Cell Aging" in these processes. For this purpose, we set two major approaches: Elucidating the hallmarks of physiological stem cell aging (A01) and the role of stem cell aging in the pathogenesis of aging-related diseases (cancer, lifestyle-related diseases, organ failure, etc.)(A02).



【Expected Research Achievements and Scientific Significance】

By focusing on "Stem Cell Aging", we will create a new research field of "Aging and diseases". Our research should provide new guidelines for prevention medicine and early intervention of aging-related diseases, and also for regenerative medicine.

【Key Words】

Stem cell, aging, aging-related disease

【Term of Project】　FY2014-2018

【Budget Allocation】　1,161,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.m.chiba-u.ac.jp/class/molmed/stemcellaging/
stemcellaging@chiba-u.jp

Title of Project：Nascent-chain biology

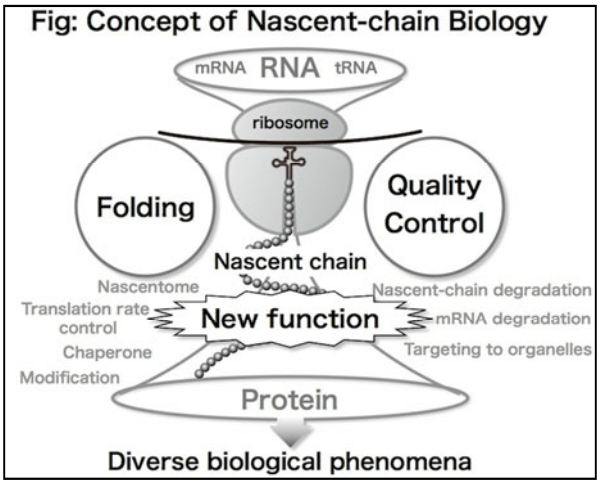
Hideki Taguchi
(Tokyo Institute of Technology, Graduate School of Bioscience and Biotechnology, Professor)

Research Project Number：26116001　Researcher Number：40272710

【Purpose of the Research Project】

Life depends on correct gene expressions. Proteins do not instantaneously finish the synthesis and folding into functioning products, but experience the nascent peptidyl-tRNAs, defined as "nascent chains", during the translation. So far, nascent chains are regarded as transient intermediates during the protein synthesis. However, recent advances have revealed that nascent chains are directly involved in a variety of cellular processes including self-maturation and the quality control system of protein and mRNA. In addition, the dysfunction of the maturation and the quality control system could perturb cellular homeostasis, often leading to human diseases.

The concept of nascent chains join the protein and RNA researchers to generate a new field called "Nascent-chain biology". Our project aims to understand the roles of the “nascent chains” in the gene expression and cellular homeostasis.



【Content of the Research Project】

[1: Nascent chain folding, modification and targeting]
-How do several chaperones cooperate or have distinct roles on nascent chain protein folding?
-How are disulfide bonds incorporated into the nascent chains?
-How are nascent chains inserted into organelle membranes?

[2: Translation speed control of nascent chains]
-What are the molecular mechanisms that cause the translation arrests or elongation speed controls?
-Are translation arrest sequences widespread in general?
-What are the physiological relevance of translation rate control?

[3: Quality control of nascent chains]
-What is the role of nascent chains in the mRNA quality control?
-What are the mechanisms by which nascent chains fold or are degraded?

[New approaches to investigate nascent chains]
-tRNA, mRNA ribosome profiling.
-Eukaryotic reconstituted cell-free translation system.

【Expected Research Achievements and Scientific Significance】

Since all proteins experience the nascent chains during the synthesis, the nascent chains are involved in a variety of biological phenomena. Understanding the nascent chains will contribute to elucidate the molecular mechanism of human diseases associated with the nascent chains.

【Key Words】

Nascent chain: Genetic information coded in DNA sequences is translated into the amino acid sequences of proteins in the ribosomes. During the translation process the ribosomes synthesize the proteins as the forms of peptidyl-tRNAs, which we call "nascent chains".

【Term of Project】 FY2014-2018

【Budget Allocation】 1,221,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pharm.tohoku.ac.jp/nascentbiology

Title of Project：Brain Protein aging and Dementia Control

Gen Sobue
(Nagoya University, Graduate School of Medicine, Professor)

Research Project Number：26117001　Researcher Number：20148315

【Purpose of the Research Project】

In our country as well, prevention and control of dementia occurring in as many as 4.6 million people are one of the most challenging issue imposed on medical sciences of the 21st century. Major molecular pathologies reside in broken neural circuits due to physiological dysfunction of proteins comprising the neural system and due to their acquisition of toxicity and pathogenicity. In the current field, we defined such toxicity-acquiring processes of functional proteins as "brain protein aging."

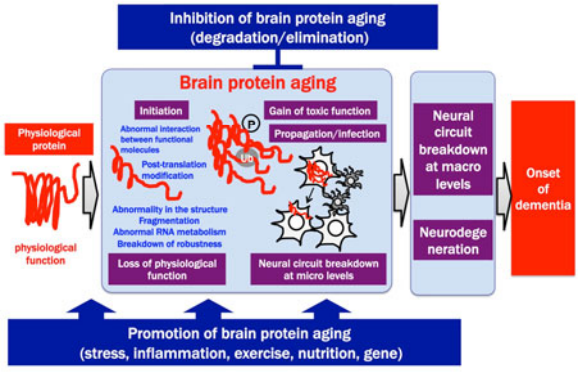


Figure 1. Brain protein aging and onset of dementia

The current research field has newly arisen to answer the following essential questions: Why brain proteins age and acquire toxicity; How neural circuits fail and bring about dementia; and What therapeutic interventions can eventually prevent dementia. This research field is expected to create a path to brain protein gerontology applying all of the next generations of advanced technologies. The study will take an interdisciplinary approach to analyze chronological changes of brain proteins, in particular, from normal to degeneration and also from various angles at the molecular to individual levels.

【Content of the Research Project】

The current field comprises "Brain protein aging and neural circuit breakdown (A01)," "Molecular basis of brain protein aging (A02)," and "Development of therapy for brain protein aging (A03)." A01 is aimed at the development of visualization of human brain protein aging and neural circuit breakdown, and specific PET imaging of aged proteins, while A02's purpose is to elucidate mechanisms of brain protein aging and neural degeneration, qualitative and quantitative constancy of proteins (robustness), and mechanisms of aged protein accumulation and its propagation and spreading. A03's task is to clarify mechanisms of brain protein aging using two innovative model systems and to clarify the aging process of brain proteins using brain imaging for Primates.

These three research projects are organically combined to accomplish the following targets: (1) Clarification of the mechanisms of initiation and pathogenicity of brain protein aging; (2) Clarification of the mechanisms of aged brain proteins' intercellular transmission and infectiveness; (3) Clarification of the mechanisms of pathogenicity acquired by aged brain proteins and its inhibition, and the development of clinical markers; and finally (4) Visualization of brain protein aging and clarification of the mechanisms of neural circuit breakdown.

【Expected Research Achievements and Scientific Significance】

Dementia and neurodegenerative disease share the molecular bases of protein aging. These molecular bases are jointly explored by a variety of researchers from basic and clinical fields of medicine with new eyes and methods. In addition, next-generation technologies are incorporated, aiming at developing novel research fields of brain protein aging. The current field will be developed as a new academic field by a eclectic mix of such researchers as those who are able to analyze functions or dynamics of brain functional proteins, those who are able to create iPS cells or primate models, those who are able to study the mechanisms of initiation, progression and removal of aged proteins, those who are able to visualize pathogenetic proteins in mice and Primates, and those who are able to evaluate and verify protein aging. Results of the current study project are expected to lead to the development of epoch-making drugs for dementia as well as other various diseases associated with brain aging.

【Key Words】
Brain protein aging, Multi-disciplinarity, Neural circuit breakdown, Protein transmission, Super-early clinical condition

【Term of Project】　FY2014-2018
【Budget Allocation】　1,169,100 Thousand Yen
【Homepage Address and Other Contact Information】
http://www.protein-dementia.jp/