Title of Project： Elucidation of mechanisms underlying glucose homeostasis mediated by inter-organ communication and development of diabetes therapies.

KATAGIRI Hideki
(Tohoku University, Graduate School of Medicine, Professor)

Research Project Number: 20H05694 Researcher Number：00344664
Keyword：inter-organ communication, glucose metabolism, diabetes mellitus

【Purpose and Background of the Research】

Metabolism in different tissues/organs is considered to be systemically regulated in a coordinated manner. In addition to humoral factors, such as hormones and cytokines, neuronal signals have recently attracted increasing attention for their roles in maintaining metabolic homeostasis at the whole-body level. We have identified several neuronal networks as being involved in inter-organ metabolic communication. A broad range of metabolic information is sent from peripheral organs/tissues and transmitted by neuronal relays consisting of vagal afferents and sympathetic efferents, resulting in cooperative metabolic regulation of functions, such as energy expenditure, pancreatic β cell mass, adaptive thermogenesis and lipid metabolism.

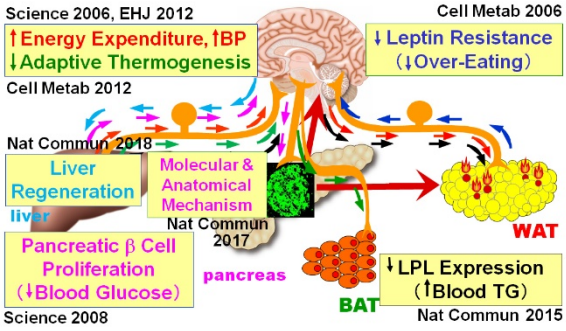

Figure. Inter-organ metabolic communications

Considering that the blood volume of an adult human is approximately 5 liters, a blood glucose concentration of 100mg/dl means that the total glucose amounts in blood is only 5 g at the whole-blood level, indicating that blood has minimal functional capacity as a glucose buffer. In particular, blood glucose levels during the fasting periods are well known to be very stable. All cells in the organs/tissues throughout the body take up and metabolize glucose as an energy source to sustain life. Moreover, since the buffering function of the blood is quite small, excesses and deficiencies of hepatic glucose release may directly induce hyper and hypo glycemia. These observations mean that hepatocytes release exactly the same amounts of glucose in total as those which are utilized throughout the body. Thus, the liver somehow knows how much glucose is consumed by remote organs in a real-time manner and continually produces and releases the right amounts of glucose. This mechanism requires great accuracy in terms of both timing and the amounts of glucose released. In this project, we aim to elucidate this mechanism.

【Research Methods】

We plan to produce inducible KO mice, in which rate-limiting enzymes catalyzing gluconeogenesis are deficient in the liver, kidney and/or small intestine and analyze metabolic phenotypes in a variety of tissues/organs. In addition, taking advantage of a new optogenetic technology which enables us to chronically activate or inactivate autonomic nerves innervating an intended tissue/organ, we aim to elucidate the inter-organ mechanism whereby the liver knows the amounts of glucose utilized throughout the body.

【Expected Research Achievements and Scientific Significance】

In this project, we aim to elucidate the fundamental mechanism which involves maintaining lives of multi-organ creatures, including human beings.

Furthermore, these exquisite mechanisms that underlie normal glucose conditions may be good targets for elucidating the causes of, and thereby novel treatments for, diabetes

【Publications Relevant to the Project】

· Uno K et al. Neuronal pathway from the liver modulates energy expenditure and systemic insulin sensitivity. Science 312: 1656-9, 2006
· Imai J et al. Regulation of Pancreatic β cell Mass by Neuronal Signals from the Liver. Science 322: 1250-4, 2008
· Yamamoto J et al. Neuronal signals regulate obesity induced β-cell proliferation by FoxM1 dependent mechanism. Nat Commun. 8: 1930, 2017
· Izumi T et al. Vagus-macrophage-hepatocyte link promotes post-injury liver regeneration and whole-body survival through hepatic FoxM1 activation. Nat Commun. 9: 5300, 2018

【Term of Project】 FY2020-2024

【Budget Allocation】 150,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.diabetes.med.tohoku.ac.jp/

Title of Project： Analysis of stemness, aging and carcinogenesis using hematopoietic stem cell ex vivo amplification system

NAKAUCHI Hiromitsu
(The University of Tokyo, The Institute of Medical Science, Project Professor)

Research Project Number: 20H05695 Researcher Number：40175485
Keyword：hematopoietic stem cell, ex vivo expansion, clonal hematopoiesis, CRISPR gRNA genome wide screening, multiomics analysis

【Purpose and Background of the Research】

Hematopoietic stem cells (HSCs) have been well studied for a long time. However, the details of the regulatory mechanisms of differentiation and self-renewal, which are the fundamental principles of stem cell biology, remain unclear due to the paucity of HSCs in the bone marrow. Most recently, we have developed and reported a method of long-term in vitro culture of mouse HSCs, a long-held dream of hematology, to expand more than 900-fold in 4 weeks while maintaining stem cell function (Wilkinson et al. Nature 2019). In this study, using the long-term HSC expansion culture method, we will attempt genome wide CRISPR screening for HSCs and mutation analysis after long-term culture. We will approach the elucidation of the mechanism of differentiation and self-renewal as well as the pathogenic mechanism of age-related hematological malignancies. Furthermore, we aim to establish a culture method that enables ex vivo expansion of human HSCs and achieve the Holy Grail of hematology.

【Research Methods】

In our ex vivo mouse HSC expansion, the purity of functional stem cells gradually decreases with long-term culture. First, FACS and transplantation experiments will be used to identify surface markers that can purify functional HSCs from the expanded cells.

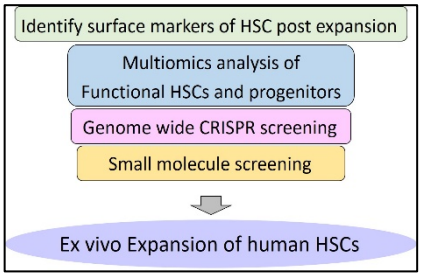

Figure 1 Research strategy

Based on this result, the true stem cell fraction is isolated and a multi-omics analysis that requires a large number of samples is performed. At the same time, comprehensive gene knockout will be performed with the CRISPR / Cas9 genome editing library to identify the signals required to maintain stem cell properties.

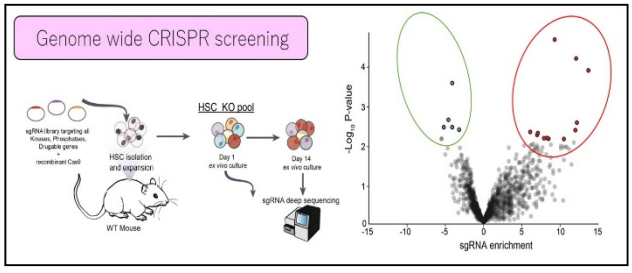

Figure 2 Genome wide CRISPR screening for HSCs

Screening for small molecule compounds, etc. will also be carried out, focusing on the identified signaling pathways. Then, by applying the obtained findings to the culture system of human hematopoietic stem cells, we aim to elucidate the nature of self-renewal of hematopoietic stem cells and the conditions necessary for amplification of human HSCs.

【Expected Research Achievements and Scientific Significance】

HSCs have been clinically applied as an established treatment for hematopoietic malignancies and hereditary blood diseases in the form of bone marrow transplantation for more than 50 years, but it is difficult to find HLA-matched donors. In addition, age-related increase in hematological malignancies is strongly correlated with the accumulation of gene mutations, and there is a high frequency of clonal expansion of HSCs in the bone marrow of the elderly, which is considered to be a pre-leukemic state. However, the mechanism from mutation accumulation to onset is unknown. It is expected that these long-standing problems in hematology will be solved by performing multi-omics analysis enabled by the long-term expansion culture system of mouse HSCs that we developed.

【Publications Relevant to the Project】

1. Wilkinson AC, Igarashi KJ, Nakauchi H. (2020). Haematopoietic stem cell self-renewal in vivo and ex vivo. Nat Rev Genet. 21(9):541-554. "PMID": 32467607.
2. Wilkinson AC, Ishida R, Kikuchi M, Sudo K, Morita M, Crisostomo RV, Yamamoto R, Loh KM, Nakamura Y, Watanabe M, Nakauchi H*, Yamazaki S*. (2019). Long-term ex vivo haematopoietic-stem-cell expansion allows nonconditioned transplantation. Nature. 571(7763):117-121. "PMID": 31142833.
3. Yamamoto R, Wilkinson AC, Ooehara J, Lan X, Lai CY, Nakauchi Y, Pritchard JK, Nakauchi H. (2018). Large-Scale Clonal Analysis Resolves Aging of the Mouse Hematopoietic Stem Cell Compartment. Cell Stem Cell. 22(4):600-607 e604. "PMID": 29625072.

【Term of Project】 FY2020-2024

【Budget Allocation】 152,600 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.ims.u-tokyo.ac.jp/sct/
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Title of Project： Elucidation of the molecular mechanism of tendon and ligament homeostasis

ASAHARA Hiroshi

(Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Professor)

Research Project Number: 20H05696 Researcher Number：70294460

Keyword：Tendons and ligaments, Mkx, motor function, gene expression

【Purpose and Background of the Research】

Tendons transmit force from muscle to bone, and ligaments function to maintain proper mobility and stability of joints. The function of tendons and ligaments is reduced with aging. Complete functional recovery of injured tendons and ligaments is difficult due to their poor regenerative capacity, which often leads to a loss of mobility in daily life. Tendon and ligament dysfunction is also known to cause musculoskeletal diseases such as osteoarthritis.

Recently, several researchers, including ourselves, have shown that the transcription factor Mkx is specifically expressed in tendons and ligaments and has an important function in tendon and ligament development.

Based on these findings, this project aims to elucidate the mechanism of tendon and ligament homeostasis and regeneration by using a combination of multiple genetically engineered mice and rats, and single-cell level molecular analysis to clarify the gene expression network via Mkx and its physiological significance in tendon and ligament homeostasis.

【Research Methods】

We will perform single-cell transcriptome analysis of mouse Achilles tendons to identify the cell groups that comprise tendon and ligament tissue and to investigate the function of each cell group by examining specific gene expression patterns.

In particular, we will extract tendon cell fractions that play a role in tendon tissue homeostasis and analyze the gene expression network of Mkx in tendon cells in detail by chromatin immunoprecipitation-sequencing analysis targeting Mkx and transcriptome analysis by conditional knockdown of Mkx genes in the cell groups.

The function of Mkx after tendon and ligament maturation will also be analyzed molecularly, histologically and physiologically by using conditional Mkx knockout mice and rats.

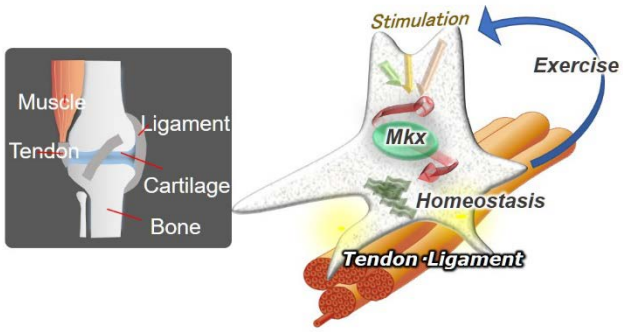
In addition, we will search for cascades that enhance Mkx gene expression and examine the maintenance of tendon and ligament homeostasis and tissue regeneration through its inactivation.

【Expected Research Achievements and Scientific Significance】

Elucidation of the molecular mechanisms important for the repair of tendon and ligament injuries may provide a basis to future reconstructive and regenerative medicine.

This study will also provide important insights into the significance of proper exercise which stimulates and improves the function of the musculoskeletal system physiological functions.

In summary, the genetic and molecular analysis of tendons and ligaments will contribute to the enhancement of healthy life expectancy in humans



The molecular basis of the tendons and ligaments

【Publications Relevant to the Project】

- Nakamichi R, Ito Y, Inui M, Onizuka N, Kayama T, Kataoka K, Suzuki H, Mori M, Inagawa M, Ichinose S, Lotz M, Sakai D, Masuda K, Ozaki T, Asahara H. Mohawk promotes the maintenance and regeneration of the outer annulus fibrosus of intervertebral discs. *Nat Commun*. 7:12503. 2016
- Suzuki H, Ito Y, Shinohara M, Yamashita S, Ichinose S, Kishida A, Oyaizu T, Kayama T, Nakamichi R, Koda N, Yagishita K, Lotz M, Okawa A, Asahara H. Gene targeting of the transcription factor Mohawk in rats causes heterotopic ossification of Achilles tendon via failed tenogenesis. *Proc Natl Acad Sci U S A.* 113(28):7840-5. 2016

【Term of Project】

FY2020-2024

【Budget Allocation】

145,000 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.tmdusystemsbiomedicine.com

【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project： **Understanding the mechanism of the cutaneous immune-diversity and its relationship with other organs**

KABASHIMA Kenji
(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number: 20H05697 Researcher Number：00362484
Keyword：Dermatology, Immunology, Allergy

【Purpose and Background of the Research】

Elucidation of the mechanism of skin immune response to external invasion leads not only to the understanding of the pathogenic mechanism of skin diseases such as atopic dermatitis, but also to the understanding of the immune response in other organs. The applicant found that lymphoid tissue construction (SALT) was induced in the skin in response to external invasion, and named it iSALT. Currently, elucidation of the physiological role of iSALT in the skin and systemic immune response is expected.

The aim of our study is: (1) Elucidate the induction mechanism of iSALT and the role of iSALT in inducing diversity of skin immune responses. (2) Understand the effect of iSALT on systemic immunity. (3) Figure out the pathophysiology of inflammatory skin diseases and the role of skin as the starting point of systemic immune control by applying the findings obtained in mice to human research.

【Research Methods】

So far, the applicant has found iSALT in the Th1 type immune response (contact dermatitis model), and its formation requires perivascular macrophages and CXCL2 produced from them, and it occurs in the posterior capillary vein region. We have already elucidated a part of the mechanism of iSALT formation, such as the induction of high endothelial venules (HEV) in the posterior capillary vein region. However, there are still many unclear points such as which subset of perivascular macrophages are involved, their activation mechanism, the involvement of forming factors other than CXCL2, and the induction mechanism of HEV. In particular, HEV is a structure that is not found in steady-state skin, and may be a tissue infiltration pathway for naive T cells, central memory T cells, etc., similar to its function in lymph nodes.

Therefore, first, we separate perivascular macrophages and vascular endothelial cells from the steady state and contact dermatitis and analyze the expression profile using the single-cell RNA sequencing method. Then we elucidate the subsets and functions of these cell types in the process of iSALT formation. Based on the results obtained there, we will identify the factors for perivascular macrophage activation, iSALT formation, and HEV formation. Then, we will try to identify new iSALT and HEV-forming factors by using specific inhibitors and conditional knockout mice of those factors. Furthermore, cells producing various morphogenetic factors will be identified using candidate cell-deficient mice to elucidate the whole picture of the iSALT formation mechanism.

【Expected Research Achievements and Scientific Significance】

In this study, we will take advantage of iSALT, which is a new secondary lymphoid construct that we have independently discovered, as a starting point to elucidate the mechanism of diversity of acquired skin immune responses and to cut into the systemic allergy progression mechanism from the skin, such as allergic march. Furthermore, we will elucidate the spatiotemporal dynamism of cell dynamics and the mechanism of inducing various immune responses by organically combining cutting-edge technologies such as skin bioimaging technology, single-cell RNA sequencing method, and mass cytometry analysis method.

If the skin immunity and systemic immune control mechanism from the skin is clarified by this study, it is expected that skin immune control will lead to control of not only skin diseases but also immune diseases in other organs.

【Publications Relevant to the Project】

・ Kabashima K Honda T, Ginhoux F, Egawa G. 2019. The immunological anatomy of the skin. ***Nat Rev Immunol*** 19: 19-30
・ Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, Kabashima K. 2018. The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. ***Nat Immunol*** 19: 1286-98

【Term of Project】 FY2020-2024

【Budget Allocation】 151,000 Thousand Yen

【Homepage Address and Other Contact Information】
http://www.kuhp.kyoto-u.ac.jp/~skin/index.html

Title of Project： Analysis of the malignant progression of tumors affected by tumor angiogenesis

TAKAKURA Nobuyuki
(Osaka University, Research Institute for Microbial Diseases, Professor)

Research Project Number: 20H05698 Researcher Number：80291954
Keyword：tumor, angiogenesis

【Purpose and Background of the Research】

It has been elucidated that merely VEGF signal inhibition has limitation for effective suppression of tumor growth. It has been widely accepted that new blood vessel formation in tumor is induced by sprouting angiogenesis under VEGF/VEGFR system; however, in our research, we will elucidate another mechanism of neovascularization in tumor (Fig. 1). Moreover, we will elucidate the mechanism how malignant progression of cancer cells such as epithelial-mesenchymal transition and contrary phenomenon is induced by angiocrine signals from endothelial cells (Fig. 2) based on the achievement of novel mechanism of vascular remodeling by endothelial stem cells.

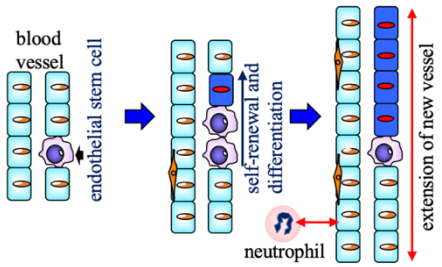


Figure 1 Molecular analysis of 'extension' type angiogenesis

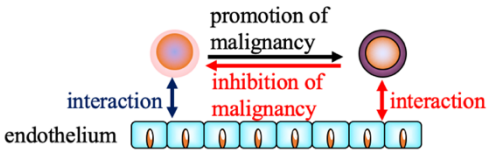


Figure 2 Elucidation of angiocrine signals in cancer

【Research Methods】

Our research can be divided into two plans. One is molecular analysis of new blood vessel formation induced by extension of pre-existing blood vessels regulated by endothelial stem cells and neutrophils (Fig. 1). The other is molecular mechanism of angiocine regulation in promoting malignant progression of cancer cells (Fig. 2). In the plan 1, we will analyze blood vessel formation in tumor which shows resistance against VEGF signal inhibitors, especially focused on the quality and quantity differences of neutrophils and endothelial stem cells. In the analysis, we will observe the time course of new blood vessel formation three dimensionally by real-time imaging using two photon microscopy. Here, we will observe the involvement of endothelial stem cells for new vessel formation by lineage tracing of these cells. In research plan 2, among molecular cues from tumor endothelial cells, we will elucidate molecular function of two molecules which are already isolated as molecules regulating malignant progression of cancer cells or inhibition of malignant change of cancer cells.

【Expected Research Achievements and Scientific Significance】

Our research shed light on the understanding malignant tumor microenvironment by analyzing the interaction of cancer cells and blood vessels. Molecular mechanism of malignant progression of cancer cells or tumor vascular formation has been independently analyzed so far. Our research will be performed to elucidate tumor malignancy in association with vascular formation. Our research will develop novel methods for cancer therapy by the suppression of interaction of cancer cells and endothelial cells.

【Publications Relevant to the Project】

· Naito H, et al. TAK1 Prevents Endothelial Apoptosis and Maintains Vascular Integrity. **Dev Cell** *48*, 151-166 (2019).
· Kidoya H, et al. Regnase-1-mediated post-transcriptional regulation is essential for hematopoietic stem and progenitor cell homeostasis. **Nat Commun**. *10*, 1072 (2019).
· Wakabayashi T, et al. CD157 Marks Tissue-Resident Endothelial Stem Cells with Homeostatic and Regenerative Properties. **Cell Stem Cell** *22*, 384-397 (2018).

【Term of Project】 FY2020-2024

【Budget Allocation】 151,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://st.biken.osaka-u.ac.jp/

【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project： Development of novel therapeutic strategies for therapy-refractory leukemia

MAEDA Takahiro
(Kyushu University, Graduate School of Medical Science, Professor)

Research Project Number: 20H05699 Researcher Number：00791972
Keyword：Acute myeloid leukemia, Acute lymphoblastic leukemia, CRISPR/Cas9 gene-editing tool

【Purpose and Background of the Research】

Adult acute leukemia is a devastating disease with a long-term survival rate of less than 40%. Why do some leukemias come back after chemo/radiotherapy? From genetic points of view, leukemia recurrence originates both at the cellular and organismal levels. At the cellular level, mutations in certain genes, such as *TP53* loss-of-function mutations, dictate poor response to chemotherapy. At the organismal level, intra- and inter-tumoral clonal heterogeneity in the genome, epigenome, transcriptome and/or proteome renders the eradication of leukemia cells by chemotherapy more challenging.

Recent progress in sequencing technologies helps unveiling a near complete picture of the leukemia genome. However, there are many unknowns as to 1) how mutated genes collaboratively function in leukemia development and progression; 2) how gene mutations affect sensitivity and resistance to drug treatment and 3) whether cancer cells with a specific mutation exhibit synthetic lethal relationships with a specific drug treatment.

Aims of this study are: to 1) identify drug targets for leukemias that exhibit poor prognosis, such as those harboring *TP53* mutations; 2) identify targets for novel combination chemotherapies and 3) to obtain the proof-of-concept evidence for developing drugs for molecules that we identify in aims 1) and 2).

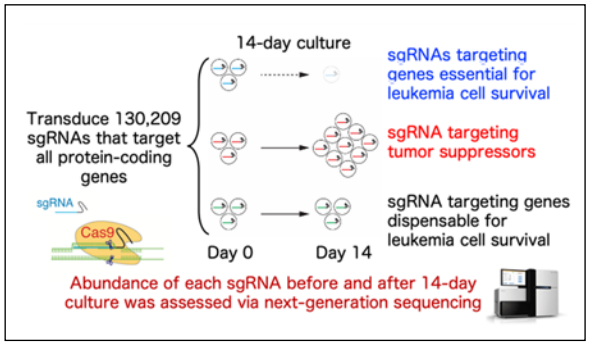


Figure 1. Genome-wide CRISPR/Cas9 screening

【Research Methods】

Genome-wide loss-of function screening using the CRISPR-Cas9 genome-editing technology is a powerful tool for functional genomics (Figure 1). However, identifying actionable targets has been challenging due, in part, to the complex genetic background of cell lines used for screening. To overcome this obstacle, we established mouse AML lines whose genetic backgrounds are well-defined (e.g. AML with *Trp53* mutations). We will perform genome-wide CRISPR/Cas9 screenings using these lines in the presence or absence of anti-AML drugs. We then elucidate molecular mechanisms behind the observed phenotypes using a series of molecular and genetic methods, including single-cell technologies, proteomics and PDX (patient-derived xenograft) models. Finally, we will determine whether the targets identified in aims 1/ 2 are amenable for drug development using the PROTAC (proteolysis targeting chimera) technology.

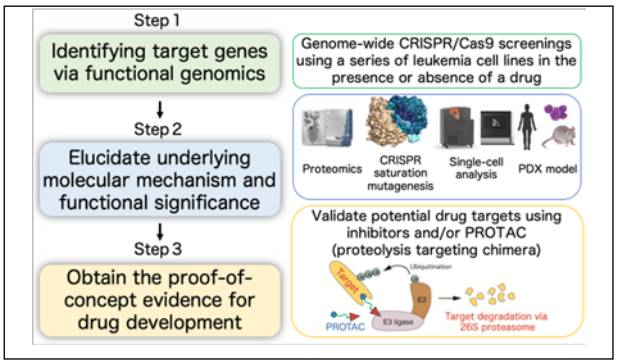


Figure 2. Overall design of the research project

【Expected Research Achievements and Scientific Significance】

We expect to elucidate molecular mechanisms underlying therapy-refractory leukemias and to identify new therapeutic targets to treat them. Our study is significant, because it may facilitate development of therapeutic strategies for therapy-refractory leukemias.

【Publications Relevant to the Project】

・ Masuda T et al. Transcription factors LRF and BCL11A independently repress expression of fetal hemoglobin. *Science*. 2016 Jan 15;351(6270):285-9.
・ Yamauchi T et al. Genome-wide CRISPR-Cas9 screen identifies leukemia-specific dependence on a pre-mRNA metabolic pathway regulated by DCPS enzyme. *Cancer Cell*. 2018 Mar 12;33(3):386-400.

【Term of Project】 FY2020-2024

【Budget Allocation】 151,300 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.lab.med.kyushu-u.ac.jp/precision/
t_maeda@cancer.med.kyushu-u.ac.jp

Title of Project： **Neurogenesis and its pathogenesis in the neonatal brain: an integrated understanding using advanced analytical techniques**

SAWAMOTO Kazunobu
(Nagoya City University, Graduate School of Medical Sciences, Professor)

Research Project Number: 20H05700 Researcher Number：90282350
Keyword：neonatal brain, neurogenesis, neural development, brain diseases, preterm birth

【Purpose and Background of the Research】

The number of patients with cerebrovascular diseases and dementia is increasing among the elderly, due to the rapid aging of the population and the declining birth rate in Japan. On the other hand, the development of perinatal care has enabled premature and preterm infants to survive, but the proportion of newborns with brain dysfunction is increasing.

New neurons, continuously generated in the human neonatal brain from neural stem cells, are thought to be involved in normal brain development and disease pathogenesis. To translate this phenomenon into therapies, we need to elucidate the mechanism of brain cell production, or "neurogenesis".

We have been studying the migration of new neurons produced from stem cells in the ventricular-subventricular zone (V-SVZ) of the postnatal brain. We have discovered various mechanisms by which neonatal neurons interact with their surrounding cells. In this study, we aim to investigate the mechanisms and pathogenesis of neurogenesis in the neonatal brain in an integrated and comprehensive manner, and to gain a more complete understanding of the mechanisms.

【Research Methods】

In this study, we will use several recently-established analytical-techniques to elucidate the interaction between migrating and maturing brain cells and surrounding cells, during the neonatal period. Three-dimensional electron microscopy (SBF-SEM) techniques will be used to reveal the fine morphology of stem cells and their surrounding cells. To elucidate the molecular mechanisms responsible for cell-cell interactions by multi-omics analysis including 3D electron microscopy, metabolomic analyses, proteome, and single-cell RNA-seq.

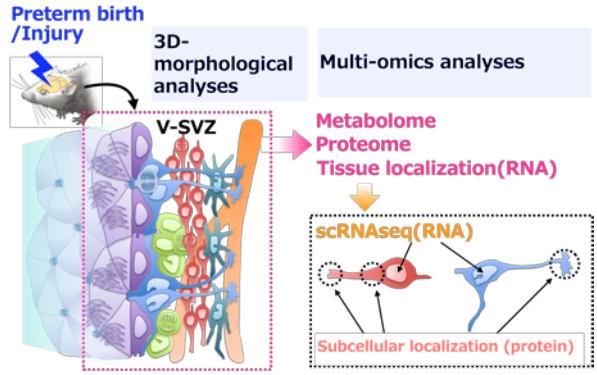


Figure 1 Methods used in this study

Shinji Saito (Nagoya City University) will evaluate the preterm birth model and provide clinical medical advice as a pediatrician, Kotaro Kimura (Nagoya City University) will analyze cell migration patterns and electron microscopy images using AI technology, and Katsura Zaitsu (Nagoya University) will conduct metabolomic analysis using PESI-MS/MS.

【Expected Research Achievements and Scientific Significance】

This study will enable us to capture the cellular architecture of the V-SVZ and morphological changes in each cell during development, as well as to comprehensively understand the mechanisms and significance of these changes at the level of genes, proteins and metabolites. The results of this research may extend beyond the scope of neuroscience to other medical and biological fields. In addition, the research may lead to the elucidation of the causes of developmental disorders and to the development of preventive and therapeutic methods, as well as providing clues to understanding the low regenerative capacity of the adult brain and contributing to the development of new treatments for intractable neurological diseases.

【Publications Relevant to the Project】

・ Jinnou H, Sawada M, Kawase K, …, Ajioka I, Saitoh S, Sawamoto K. Radial glial fibers promote neuronal migration and functional recovery after neonatal brain injury. ***Cell Stem Cell*** 22: 128-137 (2018)
・ Kaneko N, Herranz-Pérez V, Otsuka T, …, Kawaguchi Y, García-Verdugo JM, Sawamoto K. New neurons use Slit-Robo signaling to migrate through the glial meshwork and approach a lesion for functional regeneration. ***Sci Adv*** 4: eaav0618 (2018)
・ Sawada M, Ohno N, Kawaguchi M, …, Nakagawa H, Uemura A, Sawamoto K. PlexinD1 signaling controls morphological changes and migration termination in newborn neurons. ***EMBO J*** 37: e97404 (2018)

【Term of Project】 FY2020-2024

【Budget Allocation】 119,900 Thousand Yen

【Homepage Address and Other Contact Information】

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