R&D item

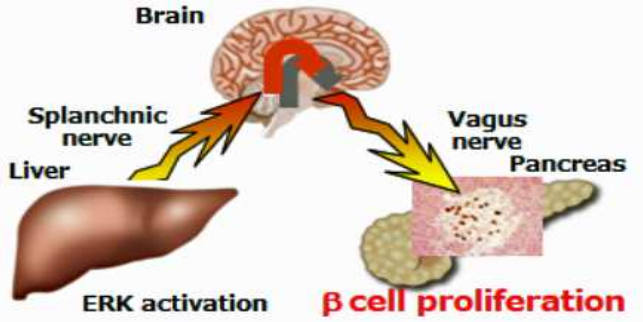
1. Elucidation of homeostatic mechanisms by inter-organ communication and development of therapeutic and diagnostic methods

Progress until FY2023

1. Outline of the project

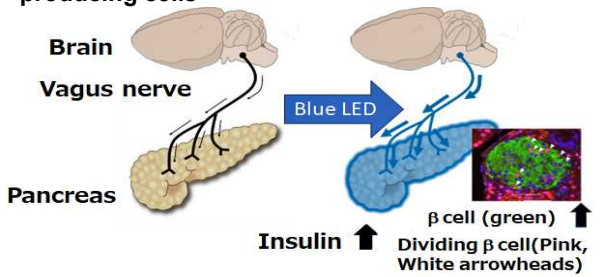
This R&D item is responsible for the project's themes of (i) elucidating the inter-organ network mechanisms (See figure below) that maintain metabolic and circulatory homeostasis, and (ii) developing new prevention, diagnosis, and treatment methods for diabetes and its co-morbidities based on these mechanisms.

To achieve this goal, we are tackling this challenging theme by conducting detailed analyses to elucidate the molecules involved in the signaling of afferent, central, and efferent nerves connecting organs and their regulatory mechanisms. With the idea of developing preventive, diagnostic, and therapeutic methods for diabetes using inter-organ networks through the nervous system, which is completely different from conventional methods, we are working on this project using single cell RNA sequencing, optogenetics, fMRI, artificial nerve connections, plasma lipidomics, and other techniques.



2. Outcome so far

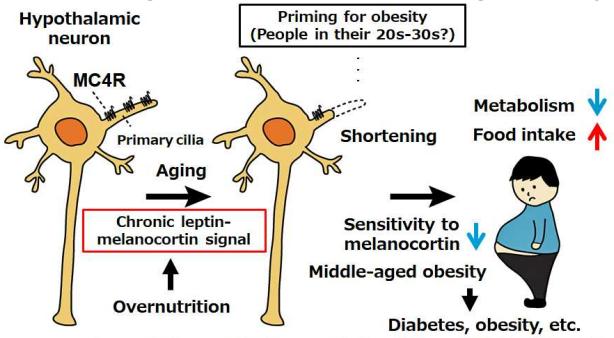
(1) Nerve stimulation of the pancreas increases insulin-producing cells



Press Release with Tohoku University and JST (2023.11.10)

This is an important achievement that demonstrates POC for the regulation of inter-organ networks and vagus nerve stimulation to the pancreas as a method of diabetes prevention and treatment.

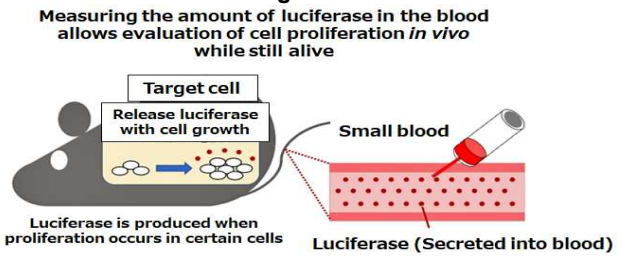
(2) Elucidating the mechanism of middle-aged obesity



Press Release with Nagoya University and JST (2024.3.7)

The results show that the length of primary cilia in the brain's neurons determines the susceptibility to obesity and that their shortening due to aging and overnutrition is the cause of middle-aged obesity. It is expected to lead to the development of preventive methods and treatments for lifestyle-related diseases at a pre-symptomatic stage.

(3) Development of mice in which cell proliferation can be observed in a living state



Press Release with Tohoku University and JST (2023.6.15)

This is the result of the development of mice in which proliferating cells can be observed alive by simply drawing a very small amount of blood when necessary. It is expected to be applied to research on treatments in various diseases, such as regenerative therapy for diabetes that increases insulin-producing cells and drug development that suppresses the growth of cancer cells.

3. Future plans

In the future, we will try to analyze glucose metabolism in epilepsy patients with implanted vagus nerve stimulator in order to validate the results of vagus nerve stimulation obtained in mice in humans. This will lead to the development of methods to prevent and treat diabetes using vagus nerve stimulation.

In addition, to elucidate the molecular mechanism of afferent activation and to control it by compounds, we will try to screen for molecules that activate afferent nerves and regulate pancreatic β cell proliferation, basal metabolic increase, and blood pressure fluctuations. This will lead to the development of methods to prevent and treat diabetes and its co-morbidities with the compounds.

R&D item

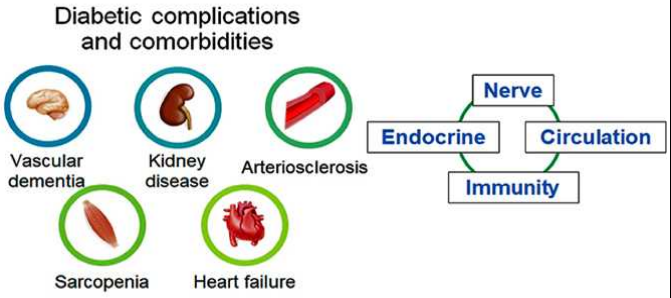
2. Elucidation and control of the mechanism of multi-organ transformation in diabetes mellitus

Progress until FY2023

1. Outline of the project

This R&D item is responsible for research within the project to elucidate the mechanisms of multi-organ transformation in diabetes (See figure below) and to develop control methods.

To achieve this goal, we are working on challenging themes in organs such as heart, liver, brain, and kidney, as well as blood vessels, where we must analyze organ transformation from both functional and morphological perspectives. Based on the idea that close interactions are involved between concomitant diseases, which is completely different from the conventional approach, we are working on this project using techniques such as single cell RNA sequencing, flow cytometry, two-photon microscopy, scanning electron microscopy, light sheet microscopy, and tissue transparency techniques.

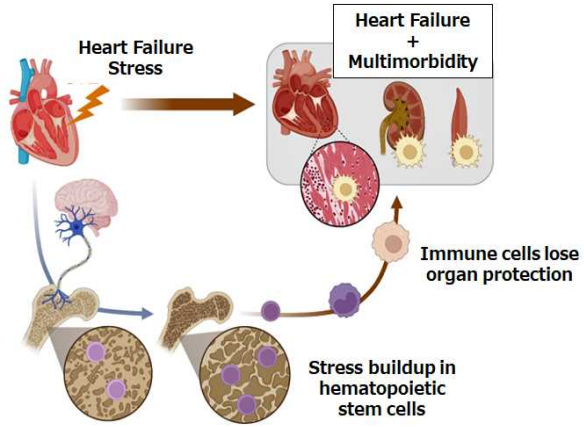


https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

2. Outcome so far

(1) Elucidating the mechanisms of recurrent heart failure and multimorbidity

Heart failure, known as a major comorbidity of diabetes mellitus, is characterized by the fact that “once a patient develops heart failure, he/she is in and out of the hospital repeatedly” and “it also affects other diseases”. This is a groundbreaking achievement that reveals the mechanism of recurrent and multiple heart failure.



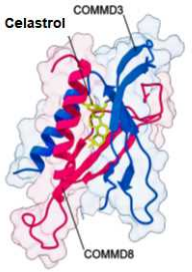
Press Release with the University of Tokyo, Chiba University and JST (2024.5.25)

During heart failure, the stress accumulates in the hematopoietic stem cells via the brain and nervous system. Immune cells supplied to various organs from hematopoietic stem cells that have accumulated stress lose their protective effect on each organ, resulting in multiorgan failure. It is expected to lead to the development of methods to prevent recurrence of heart failure.

(2) Discovery of a link between ketone body production and the development of sarcopenia

The results show that decreased ketone body production in the proximal tubules of the kidney may be involved in the development of sarcopenia, a diabetic comorbidity, as well as decreased urine concentrating ability in the elderly.

(3) Discovery of plasmablasts in adipose tissue



Osaka University Press Release (2023.3.22)

Plasmablasts, which are strongly implicated in inflammatory diseases, were detected in B lymphocytes in the epididymal fat of obese mice. Celastrol, an inhibitor of the COMMD3/8 complex, was found to inhibit plasmablastogenesis. Since celastrol has anti-obesity and glucose tolerance improving effects, inhibition of COMMD3/8 complex function may be able to control the pathogenesis of diabetes mellitus.

3. Future plans

In the future, we will try to analyze single cell RNA sequencing of cardiac tissue macrophages, hematopoietic stem cells, and peripheral blood to clarify the effects of high-fat diet load on hematopoietic and immune systems. This will help to elucidate the mechanisms of how metabolic abnormalities affect the hematopoietic and immune systems, and to identify diagnostic and therapeutic targets for diabetes complications.

To further elucidate the link between ketone body production in the kidney and the development of sarcopenia, we will also try to analyze whether mice that overexpress ketone bodies in the proximal tubules improve sarcopenia. This will allow us to explore the possibility of preventing and treating diabetes complications by targeting ketone body metabolism.

Furthermore, to elucidate the role of the fenestrae in liver sinusoidal endothelial cells, we will try to elucidate the regulatory mechanisms of the size and number of the fenestrae. This will allow us to determine whether the size and number of fenestrae are involved as a mechanism for determining postprandial blood glucose levels.

R&D item

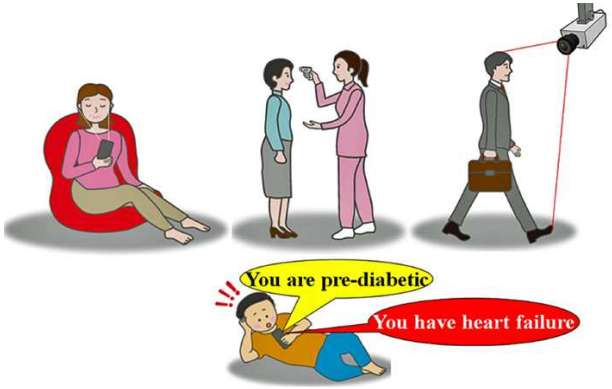
3. Development of technology for easy acquisition of biometric data in humans and analysis of human data

Progress until FY2023

1. Outline of the project

This R&D item is responsible for the development and social implementation of a method to detect and predict the early stages of diabetes and its co-morbidities as simply and non-invasively as possible based on the analysis of biological information, genome, and hepatic glucose uptake capacity using contact and non-contact devices (See figure below).

To achieve this, we are working on creating a highly accurate early diabetes detection algorithm, improving the accuracy of the Diabetes Omnigenic Model, and collecting data from the $^{13}CO_2$ breath test as challenging themes. We are working on the concept of early detection of diabetes and heart failure from non-invasive devices only, which is completely different from conventional methods, using high-speed spectral cameras, AI, cohort data analysis, and other methods.



https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

2. Outcome so far

(1) Construction of an algorithm for early detection of heart failure at home

Using contact devices (ECGs and Apple Watches that can be used at home), we created an algorithm for early detection of heart failure at home and proceeded to intellectual property (IP) in Japan and overseas.

(2) Construction of an algorithm to detect diabetes

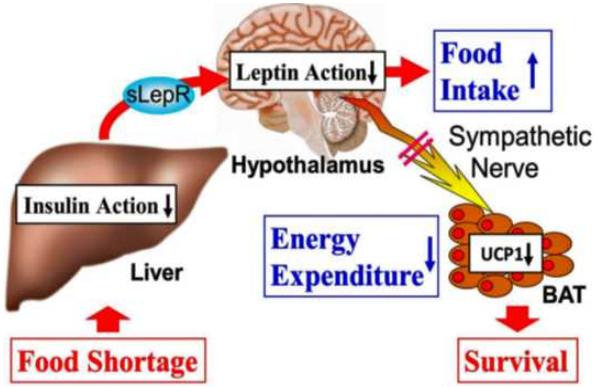
Using a non-contact device (high-speed spectral camera), we have developed an algorithm for detecting diabetes in addition to an algorithm for detecting hypertension at an early stage. We are working on IP.

(3) Examination of glucose oxidation and hepatic glucose disposal capacity using the $^{13}CO_2$ breath test

We have intellectualized the ^{13}C-glucose breath test, which tests glycoxidation capacity at the individual level by measuring $^{13}CO_2$ emitted in the exhaled breath after ingestion of ^{13}C-glucose.

(4) Uncovering the mechanisms from the liver that survive hunger and protect lives

This is the result of the discovery of a life-preserving mechanism in which the liver plays a key role in reducing caloric consumption beyond what is necessary during starvation and increasing appetite. Soluble leptin receptors are secreted from the liver in response to decreased insulin signaling. The findings are expected to lead to applications in ways to prevent diabetics from overeating.



Tohoku University Press Release (2023.4.24)

3. Future plans

In the future, we will further collect data from humans to enable early detection of hypertension and diabetes by non-invasive devices, and will try to tune the algorithm. By doing so, we aim to build algorithms that can withstand social implementation for the general public.

For the $^{13}CO_2$ breath test, we will also try to accumulate data on a 75 g ^{13}C -glucose load in order to link it to the data related to life expectancy obtained in the Ohasama cohort. This will allow for further matching with the life span-related results obtained in the Ohasama cohort.

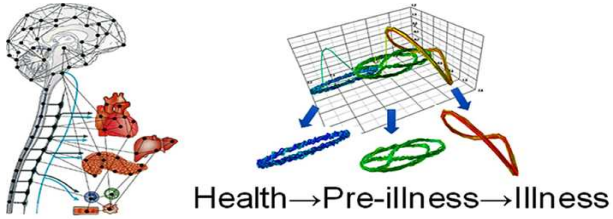
R&D item

4. 5. Understanding homeostasis through mathematical model analysis and its applications, Understanding the pre-symptomatic stage of diabetes and its complications and building a database

Progress until FY2023

1. Outline of the project

The two R&D item (items 4 and 5) play two roles in the project: (i) to collect various data over time on the transition from the normal or pre-symptomatic stage to the diseased state, focusing on type 2 diabetes and its concomitant disease, heart failure (item 5), and (ii) to use these animal experimental data and human biological data to advance mathematical model analysis to extract key elements for a comprehensive understanding.



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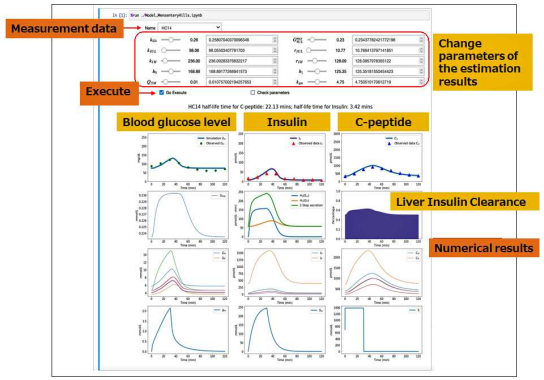
To achieve this, close collaboration between mathematical scientists and medical and biological researchers is a challenge. We are working on the concept of linking experiments/data acquisition with model analysis using various methods such as biochemistry, gene expression, epigenomics, metabolomics, organ-specific functional analysis, and mathematical model analysis.

2. Outcome so far

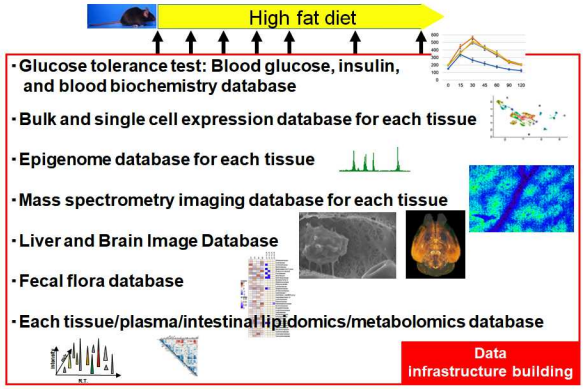
(1) Implementation of glucose tolerance test simulator

We have developed an oral glucose tolerance test simulator using a 9-compartment model that allows easy parameter manipulation. This simulator makes it possible to evaluate changes in blood glucose and insulin levels and



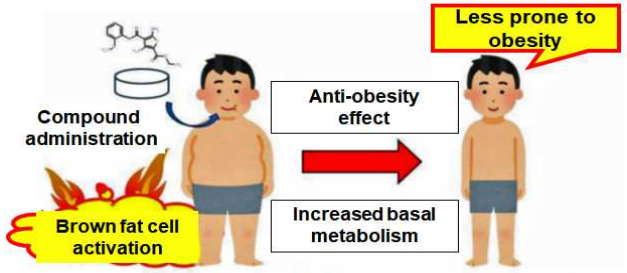
the metabolic state of each organ by changing various parameters.

(2) Acquisition of mouse data for time series analysis of pre-symptomatic states



We load mice with a high-fat diet and accumulate biochemical data over time, gene expression and epigenomic data for each organ, metabolomic data for organs and blood, fecal analysis data, and site-specific functional data for the liver and brain.

(3) Discovery of a novel anti-obesity drug candidate that reduces weight gain by increasing heat production



Iwate Medical University Press Release (2024.1.24)

From the search for compounds that increase heat production in adipocytes, we have found compounds that exhibit anti-obesity effects in animal experiments. It is expected not only to lead to weight loss, but also to therapeutic applications for various diseases such as diabetes, dyslipidemia, and fatty liver related to obesity and metabolic syndrome.

3. Future plans

In the future, by focusing on glucose and insulin metabolism in each compartment, we will try to capture diabetes-specific changes in metabolism and find the key factor parameters that cause these metabolic changes. This will allow us to mathematically clarify the mechanism of diabetes development in mice.

In addition, to construct mathematical modeling using data from pre-symptomatic stage analysis, we will try mathematical modeling focusing on the relationship between intestinal microbiota and obesity. This captures the parameters of the transition from health to disease and searches for candidate factors for pre-symptomatic stage.