R&D item

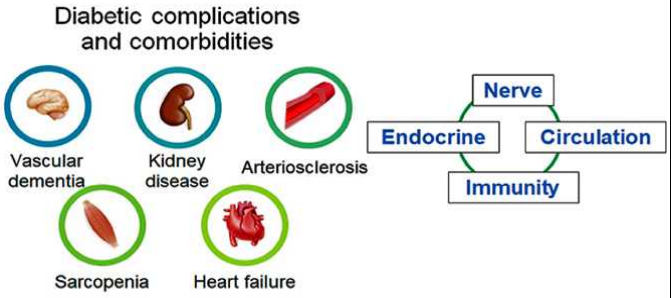
2. Elucidation and control of the mechanism of multi-organ transformation in diabetes mellitus

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.

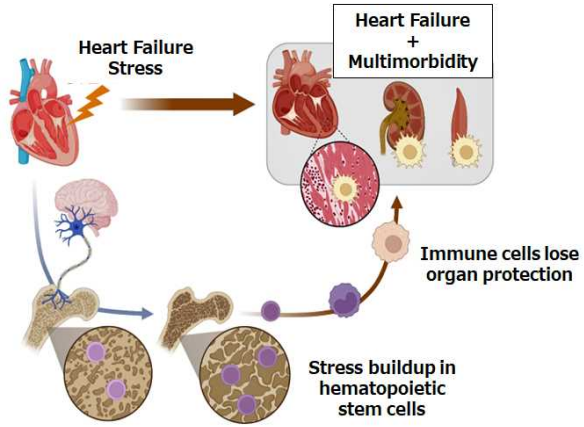


https://www.moonshot-katagiri.proj.med.tohoku.ac.jp/research-e.html

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.



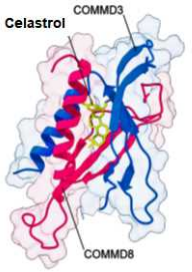
Press Release with the University of Tokyo, Chiba University and JST (2024.5.25)

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.