R&D Theme

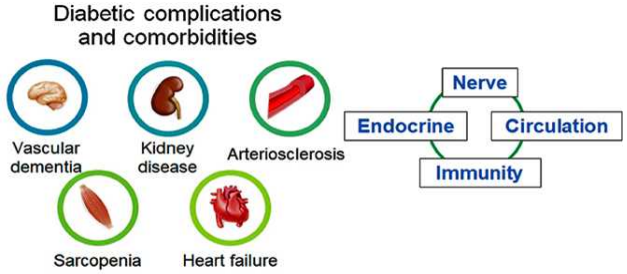
Elucidation and control of the mechanism of multi-organ transformation in diabetes mellitus

Progress until FY2022

1. Outline of the project

This R&D theme 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) Discovery that sympathetic neuropathy caused by heart failure deteriorates hematopoietic stem cell differentiation

(2) Discovery that bone marrow transplantation of mentally stressed mice induces heart failure and increases stress vulnerability in kidney and skeletal muscle

(3) Discovery of the presence of plasmablasts in adipose tissue

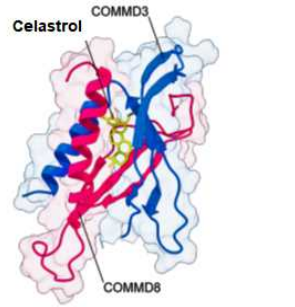
(4) Establishment of a spatiotemporal analysis method for the flow of red blood cells and plasma in the cerebral microcirculation

(5) Elucidation of the mechanism from the liver that survives starvation and protects life (right figure)

(6) Elucidate the role of ketone body production by the proximal tubule in maintaining renal function

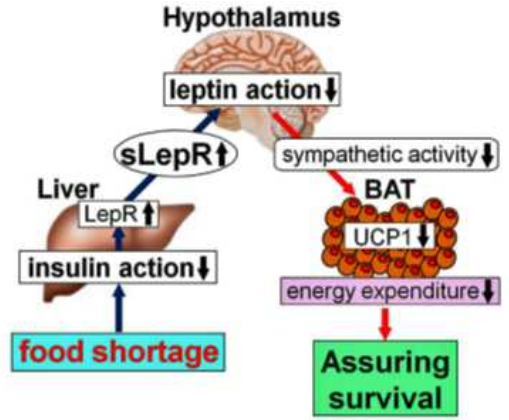
(7) Creation of a multi-organ whole-cell atlas and quantification of the degree of organ damage

In the above, (1) is a discovery that leads to the elucidation of the mechanism by which bone marrow transplantation in heart failure mice causes heart failure and multi-organ damage. (3) will lead to the elucidation of new mechanisms of metabolic deterioration caused by obesity. A control agent (Celastrol) has already been identified (left figure). (5) discovered a life-preserving mechanism in which the liver plays a key role by reducing calorie consumption beyond what is necessary during starvation and increasing appetite. It has been reported that increased appetite tends to occur when blood glucose levels are elevated, and this finding may be one of the reasons for this, and is expected to lead to applications to methods to prevent diabetic patients from overeating.



Osaka University Press Release (2023.3.22)

Inter-organ insulin-leptin signal crosstalk



Tohoku University Press Release (2023.4.24)

3. Future plans

In the future, we will analyze cell-cell interactions in the heart to elucidate the mechanism of homeostasis by macrophages and how the alteration of macrophage function induces pathological conditions such as heart failure. This will lead to the development of diagnostic and preventive methods.

In addition, to elucidate the role of the fenestrae of hepatic sinusoidal endothelial cells, we will analyze the porosity of the fenestrae in more detail and elucidate its regulatory mechanism. This will allow us to clarify whether the porosity of the fenestrae is involved in the mechanism that determines blood glucose levels in the early phase after glucose loading.