R&D item

2. Experimental Approach to Complex Control System between Organs

Progress until FY2023

1. Outline of the project

Our R&D item has the following three objectives:

1. To Promote the project by applying mathematical methods to our health sciences research with respect to the pre-disease states in collaboration with the Mathematical Approaches Team within the project.
2. To lead the realization of ultra-early precision medicine through medical intervention in the pre-disease states.
3. To build a pre-disease database by collecting temporal and comprehensive biological information on multiple organs in animal models and humans.

Specifically, we are conducting validation of mathematical methods such as DNB analysis applied for health sciences using animal models and clinical samples. We are also providing pre-disease datasets to the GakuNin RDM through the project's Mathematical Collaboration Team.

2. Outcome so far

Functional analysis of DNB genes selected through collaborative research within the project

We performed functional analysis of 15 DNB genes selected from the adipose tissue dataset of spontaneously developing metabolic syndrome (TSOD) mice by the control theory in collaboration with Prof. Jun-ichi Imura's group (Tokyo Institute of Technology) using the fruit fly model system in metabolism. We knocked down each DNB gene in the adipose tissue of flies and identified two genes, which ameliorates (gene X) and female-specifically mimic (gene Y) the effects of high fat diet feeding. We reported the effectiveness of the *Drosophila* model system in combination with DNB theory to identify the functional genes on Mebyo (Akagi *et al.*, *Cells*, 2023).

② Inter-organ network of TSOD mice and pre-disease dataset of HFD-fed C57BL/6 mice

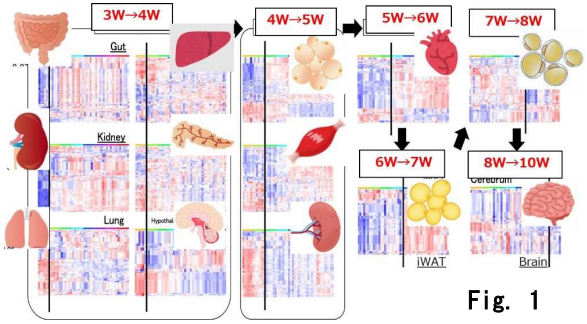

Fig. 1

To reveal the inter-organ network, we investigated how changes in gene expression propagate among organs in TSOD mice (Fig. 1). We also obtained comprehensive gene expression data and registered them to the pre-disease database from 13 organs of diet-induced obese mice (C57BL/6) at 16 time points.

③ Detection of precancerous state (pre-disease state) of hematopoietic tumors using Raman microscopy

We applied DNB theory and energy landscape analysis (ELA) in collaboration with Prof. Naoki Masuda's group (State University of New York) to Raman spectra obtained from plasma cells of the bone marrow of patients with hematopoietic tumors. The DNB analysis identified MGUS as a pre-disease state in the progression of the multiple myeloma stage (Fig. 2a).

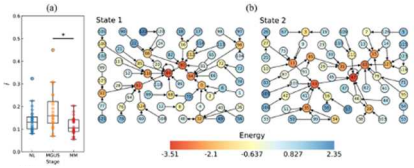

Fig. 2

The ELA revealed two stable states: the normal stage and multiple myeloma in the progression (Fig. 2b). We published two papers on validating the detection of pre-disease states using Raman spectroscopy, DNB theory, and ELA for human samples. (Oshima *et al.*, *Int. J. Mol. Sci.* 2023, Yonezawa *et al.*, *Int. J. Mol. Sci.* 2024).

④ Biology of DNB genes detected in IBD model

To investigate the biological significance of the 27 DNB genes in inflammatory bowel disease (IBD), we calculated control theory-based DNB intervention scores in collaboration with Prof. Jun-ichi Imura's group and investigated the expression of DNB genes in patients with IBD using GEO database. Then, we performed the intervention in Wars and found that Wars may play a protective role against IBD. A patent application has been filed with JST on these results.

3. Future plans

We are working on more detailed single cell analysis and intercellular network analysis using visceral adipose tissues from high-fat diet-induced metabolic syndrome mice and humans. In addition, by improving the Raman microscope, we are also developing a clinical examination system that can be applied to detect the pre-disease state of human hematopoietic tumors. Moreover, the detailed biology of Wars as a candidate intervening gene will be further investigated in mice and humans.