Session Title: Trans·Omics workshop – The 3rd International Symposium for Trans·Omics –
Organizers: Shinya Kuroda (University of Tokyo, Japan) Mariko Okada (Osaka University, Japan)
Synopsis: The life system is a "trans·omic" network, consisting of interactions between numerous molecules across multi·omic layers, such as genome, transcriptome, proteome, and metabolome. Lifestyle diseases can be regarded as complex multifactorial diseases caused by breakdowns in a trans·omic network rather than breakdown of a single molecule. Due to recent advances in methods of measurements and analyses for single·omic layers, trans·omic analyses integrating multi·omic data are in state-of-the-art development. We hold this workshop to discuss new trans·omic technologies and advanced interpretation of multi·omics data.

Program (speakers and allotted time):
14:00 ~ 14:05 Opening Remarks (5 min)
14:05 ~ 15:05 Session I (2 talks)
14:05 ~ 14:40 Matthias Heinemann (Univ. Groningen, Netherlands)
Title: Unraveling the traffic through the highways of metabolism
The metabolic fluxes in cells emerge from environmental factors and various regulatory mechanisms. Knowing these fluxes, i.e. traffic through the highways of metabolism, is key for fundamental and applied research. However, our current methods to experimentally resolve metabolic fluxes, based on 13C labeling experiments, still have a number of severe limitations. Here, I will introduce a new method to map the metabolic fluxes with unprecedented precision. In this method, we integrate metabolome, physiological and 13C labeling data with reaction stoichiometry, thermodynamic laws and constraints, using highly complex regression and sampling approaches. At this point, where we then know the metabolic fluxes, I will show results of our recent effort towards understanding the logic of the ‘traffic control system’ that governs metabolism. Specifically, I will present evidence that cellular metabolism might be constrained by the rate at which cells can dissipate Gibbs energy to the environment. This newly identified constraint has to potential to lead us to a radically new understanding of how cells function.
14:40 ~ 15:05 Mariko Okada (Osaka Univ., Japan)
Title: Analyze immune response using Omics and imaging
Gene expression is controlled by multi·omics layers. To understand gene regulatory mechanism, we analyze omics data using a mathematical model by focusing on transcription factor dynamics in B cell. Our study combined with bioinformatics and modeling and validation analysis using live cell imaging indicated that the cooperativity in enhancer regulation is important for quantitative control of target gene expression in B cell differentiation.
15:05 ~ 15:20 Coffee Break (15 min)
15:20 ~ 16:45 Session II (3 talks)
15:20 ~ 15:45 Shinpei Kawaoka (Kyoto Univ., Japan)
**Title:** Dissecting significance of single gene expression rhythm via enhancer genetics and multi-omics analyses

Circadian gene expression rhythm is disrupted in various diseases. We recently found that breast cancers distantly rewire hepatic circadian transcriptome and cause a series of physiological alterations such as hepatomegaly (enlarged liver). Yet, whether the rewired circadian rhythm is a cause for physiological alterations remains unknown. To address this issue, we aimed to disrupt expression rhythm of single gene via deletion of genomic enhancers. Enhancers are non-coding genomic elements that determine spatio-temporal gene expression patterns. Enhancer deletion when properly done enables us to ablate specific gene regulation for example rhythmic expression in vivo. We successfully obtained single rhythm-deficient mice and performed multi-omics analyses on the mutant. In the talk, I would like to discuss how the deficiency of single gene expression rhythm impacts liver physiology (multi-layered network) at the gene, protein, metabolite, and phenotypic levels.

**References**

15:45 ~ 16:10  Fumio Matsuda (Osaka Univ., Japan)

**Title:** Trans-omic analysis of the central metabolism of *Saccharomyces cerevisiae* by integration of metabolome, metabolic flux, and proteome data

**Introduction:** In the living organisms, homeostasis of the central metabolism is maintained by coordinated regulation of the metabolic system. A failure of the metabolic homeostasis would cause severe cellular phenotypes. However, a relationship among the gene deletion, the metabolic adaptations to maintain the homeostasis, and resultant phenotypes such as slow rates of cell growth remains unclear. To address the relationship, we investigated metabolic adaptation mechanisms in the knockout strains of *S. cerevisiae* lacking the central metabolism-related genes.

**Results and discussions:** A transomics dataset including fermentation profile, intracellular metabolic flux distribution, enzyme abundance, and metabolite concentration was obtained from a wild type *S. cerevisiae* and 11 single-gene deletion strains. The transomics data confirmed that the ATP homeostasis was one of the core homeostasis since the ATP concentration was the least fluctuating metabolic features. The data also showed that the single gene deletion strains commonly employed two metabolic adaptation mechanisms. In *pfk1A* and *gcr1A*, ATP shortage by the malfunction of the EMP pathway was complemented by activation of the oxidative phosphorylation. In other mutant strains,
their growth was voluntarily reduced to avoid metabolic imbalance such as by the Gcn4p dependent control of the cell component biosynthesis.

16:10 ~ 16:45 Jason Locasale (Duke Univ., USA)
**Title:** Using metabolomics and computational biology to study metabolism in health and cancer

This presentation will discuss efforts to understand glucose and amino acid metabolism in cancer biology using metabolomics approaches and mathematical modeling. First I will discuss new work on mechanisms of de novo acetate production in mammals. I will discuss work on dietary influences on the activity of metabolic pathway and relations to metabolic health and cancer. As an example, I will discuss how methionine restricted diets may allow for interventions in cancer treatment will also be discussed. This concept also provides a link between nutrient status and chromatin biology which I will briefly touch upon.

16:45 ~ 16:55 Coffee Break (10 min)
16:55 ~ 17:55 Session III (2 talks)
16:55 ~ 17:20 Katsuyuki Yugi (RIKEN, Japan)
**Title:** Dose-selective metabolic regulation by insulin across multiple omic layers

Insulin selectively regulates multiple cellular functions via its concentrations and temporal patterns. However, the cellular network that realizes selective responses to the insulin concentrations remains poorly understood. Here we reconstructed dose-selective networks of insulin action over multiple omic layers based on time-series measurements of phosphoproteome, transcriptome, and metabolome in rat hepatoma Fao cells stimulated by multiple insulin doses. In the reconstructed network, we identified two ‘trans-omic’ regulatory axes that respond to high and low doses of insulin in a mutually exclusive manner: a high-dose responsive ERK regulatory axis and a low-dose responsive AKT regulatory axis. High dose insulin signals were transmitted by ERK via the immediate early genes (IEG) to the upregulated genes. On the other hand, the low-dose insulin signal was transmitted by AKT to its target genes. Furthermore, we found that the ERK regulatory axis mainly regulates gene expression at the transcription level, whereas the AKT regulatory axis regulates gene expression at the translation level. This study reveals the system by which the liver cells interpret physiological insulin signals and regulate various cellular functions.

17:20 ~ 17:55 Uwe Sauer (ETH Zurich, Switzerland)
**Title:** Metabolic Coordination Through Metabolite-Protein Interactions

How do bacteria know what goes on in their environment and how do they make appropriate decisions? While some bona fide extracellular sensors are known, there are far more environmental conditions and cellular responses than could possibly be dealt with through dedicated sensors. Instead, most microbial responses are based on direct intracellular consequences of environmental changes. One of the first affected networks to
just about any extracellular change is metabolism that passively responds to nutritional or chemical/physical challenges. Since fluxes and intracellular metabolite levels respond within seconds, allosteric binding of metabolites to regulatory proteins and enzymes is a highly effective and rapid sensing mechanism. Different from well-establish methods to assess physical interaction between proteins and between proteins and nucleic acids, however, methods to assess metabolite-protein interactions are still in their infancy. At present we know on the order of 1500 unique regulatory metabolite-protein interactions (1). Using limited proteolysis mass spectrometry (2) and NMR (3), we have recently begun to systematically map out the physical interactions space in *E. coli*. Even for the well-investigated central metabolism we more than doubled the known metabolite-protein interactions (3). Beyond mapping the regulation network, I will focus on the even more challenging and conceptual problem: understanding which of the many regulation mechanisms actually matter for a given adaptation to elicit an appropriate physiological response.


17:55 ~ 18:00  Closing Remarks (5 min)

Registration : No registration is needed