HMT Newsletter

Friends and Colleagues,

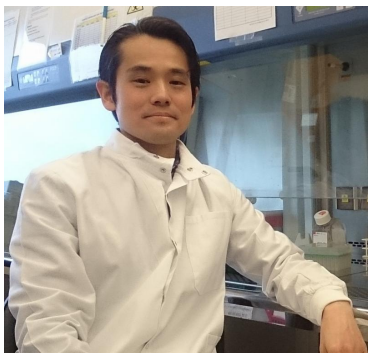
Summer is officially here in Boston and the field of metabolomics continues to grow hot as well. In this month's issue we have an interview with Dr. Kato, who recently published on the metabolic changes associated with dislocation of implanted leukemia cells. Dr. Kato shares his insights into his work and the contribution of metabolomics.
While we publish much on cancer metabolism, other areas of metabolomics continue to grow as well. In this issue we share 3 articles reflecting increasing interest; gluconeogenesis in Type-2 diabetic mice, intestinal metabolism in gnotobiotic mice and malolactic fermentation in sweet sake.

Sincerely,

Alexander Buko, PhD
Vice President
Human Metabolome Technologies America

HMT special interview

Dr. Itaru Kato
Department of Pediatrics, Kyoto University Hospital



On April 19th, Dr. Kato, published in *Blood* the article titled "Hypoxic Adaptation of Leukemic Cells Infiltrating the CNS Affords a Therapeutic Strategy Targeting VEGFA". In this article, he employed HMT metabolic profiling analysis to reveal a metabolic phenotype of patient leukemic cells transplanted to mouse model. We asked Dr. Kato about his approach to the development of leukemia therapies and the value of metabolic profiling for such purposes.

HMT: In your recent publication, you wrote about the molecular characterization of B-lineage acute lymphoblastic leukemia(B-ALL) cells in bone marrow (BM) and central nervous system (CNS) harvested from patient and xenografted mouse models. Using metabolomics, genetics and phenotypic analysis, what are your new findings in this area?

Dr. Kato: Blood cancer cells are circulating within the whole body, therefore it has not thought that these cells show specific adaptation to certain organs or microenvironment other than BM. In this study, we have established a mouse model implanted with patient leukemia cells originating from BM and compared cellular phenotype of leukemic cells in BM and CNS. By using gene expression and metabolic profiling, we have identified changes in leukemia cellular phenotypes.

HMT: What are the key changes for such cellular phenotypic changes?

Dr. Kato: We have identified that hypoxic adaptation is the key factor. Actually, it has been reported that leukemic cells in CNS show a dormant phenotype which probably relates to higher treatment resistance, but the detailed mechanisms are unknown. From this study, we have revealed that the phenotype is defined as cells with an anaerobic adaptation which includes the activation of hypoxic adaptations such as increased glycolysis.

HMT: How did metabolomics contribute to your study?

Dr. Kato: The data from metabolic profiling proposed a clear description of changes of cellular phenotype. Regarding the adaptations to hypoxia, although the gene expression pattern had suggested some changes in aerobic metabolism, it was not conclusive or able to point to a more detailed understanding. On the other hand, the changes in the metabolic profiling illustrated clear alterations in key pathways regulating aerobic adaptation, such as glycolysis. Additionally, the quantitation of the glycolytic intermediates enabled us to better describe and understand the significance of those changes. We have employed multiple techniques for the characterization of cellular phenotypes, for example, cell cycle or surface marker proteomics, however, metabolic profiling is a new and powerful tool for this purpose providing more detailed molecular descriptions.

HMT: What are the merits of specifically using HMT metabolite profiling services for this and future projects?

Dr. Kato: One of my colleagues had already utilized HMT profiling and recommended the analysis to me. For me, the biggest value was in the discussions with the HMT research coordinator regarding data interpretation. Based on the profiling data, he proposed a hypothesis for the interpretation of the observed metabolomic changes that I could incorporate into my own understanding of the events. Actually, this was my first opportunity to use metabolic profiling and his support was very effective and saved me a lot of time from trying to interpret the results.

HMT: What are the value and challenge of metabolomics, or HMT's service, for immune cell studies?

Dr. Kato: Characterization of cell phenotypes is one of the key steps in understanding cancer, especially in blood cancer research, where we are looking for novel biomarkers to

complement surface protein markers or circulating cytokines. The direct monitoring of intracellular metabolism looks to be one of the candidates for future studies to further develop biomarkers. On the other hand, I feel there are still some limitations in the preparation of specifically immune related samples for metabolic profiling, including the limited amount of cells, so I am hoping to see improvements for the development of this technology in near future.

HMT: What is in the future for your research?

Dr. Kato: In my work, we have carefully evaluated a leukemia xenografted mouse model, including histology, invasive cell patterns, cell cycle *etc*., and we have also proposed phenotypes based upon gene expression and metabolic profiling of the mouse model were confirmed in patients. Therefore, we have concluded that our model can be employed for translational research reflecting a patient pathology. As a practicing medical doctor, I always set my research goal to advancing patient treatment. For this research, the metabolic phenotypes discovered should help us create new targets and novel strategies against leukemia.

- We thank Dr. Kato for his time and continued research on leukemia. We look forward to our continued work together.

References

1) Hypoxic adaptation of leukemic cells infiltrating the CNS affords a therapeutic strategy targeting VEGF. *Blood*, **129**, *pp*. 3126-3129, 2017.

Itaru Kato, M.D., Ph.D.

Dr Kato earned his PhD in Kyoto University and worked at UCL Cancer Institute (University College London) as a Research Associate from 2014 to 2016. Now he is working at Kyoto University Hospital as a Assistant Professor of Department of Pediatrics.

HMT Updates

Featured articles

Metabolic profiling of agricultural products can often reveal novel therapeutic potential. Here, we would like to introduce recent applications in the area of food science.

Ginseng berry improves hyperglycemia by downregulating hepatic gluconeogenesis and steatosis in mice with diet-induced type 2 diabetes.

Kim M., *et al.*, *Journal of Functional Foods*, **35**, *pp*. 295-302.

Ginseng berry (GB) is known to improve obesity-induced hyperglycemia and insulin

resistance, but its mechanism is still largely unknown. Here, the authors illustrated changes in liver metabolic profiles together with changes in gene expression profiles, which were induced by dietary supplementation of GB. In the gluconeogenic pathway, metabolites such as glucose-6-phosphate and dihydroxyacetone phosphate were significantly reduced and these changes are thought to be regulated by AMPK signaling.

Differences between live and heat-killed bifidobacteria in the regulation of immune function and the intestinal environment.

Sugahara H., *et al.*, *Beneficial Microbes,* **8**, *pp*. 463-472.

Heat-killed probiotic strains have been known to elicit physiological changes however the differences between live and heat-killed probiotics have not been well elucidated. The authors investigated the effect of the treatment on immune function, intestinal metabolism and gene expression profiles by using a gnotobiotic mouse model. Live probiotics had a stronger effect on the modulation of intestinal metabolism compared to the heat-killed strains. However, both strains had immune-modulating effects.

Metabolite profile of koji amazake and its lactic acid fermentation product by Lactobacillus sakei UONUMA.

Oguro Y., *et al.*, *Journal of Bioscience and Bioengineering,* **124**, *pp*. 178-183.

Koji amazake, a traditional sweet Japanese beverage, has been consumed for over a thousand years, nonetheless, it's main composition is largely unknown. The authors analyzed the metabolites of koji amazake which was isolated from snow caverns. From two types of different fermentation processes, 300 compounds were detected and some nutrients were identified to help characterize the malolactic fermentation. Moreover, acetylcholine, a well-known neurotransmitter, was found as a result of only one specific fermentation process.

Edited by Takushi Oga, PhD

Human Metabolome Technologies America
24 Denby Road, Suite 217, Boston, MA 02134, USA | p. 617-987-0554 | f. 617-902-2434
hmtamerica@humanmetabolome.com | humanmetabolome.com/en