HMT Newsletter

Dear Friends,

Welcome to the HMT November newsletter. I attended BIO Europe 2015 in Munich last week and met many friends both old and new. I am sure those of you who attended the event will agree with me that the event was well organized and very informative. I am looking forward to next year's event. At BIO Europe I learned that there is a big demand for metabolomics analysis and HMT's unique services. HMT is committed to providing high quality data to scientists worldwide. I would like to thank those people and organizations who supported HMT's activities in Europe. Looking forward to our future work together.

Sincerely,

Tsutomu (Tom) Hoshiba
CEO
Human Metabolome Technologies America

HMT Updates

Conference Report

AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics
November 5 - 9, Boston, Massachusetts, USA

HMT was pleased to attend the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. It is clear that a new phase of immuno-based therapies is at the forefront of cancer therapeutics and have been approved for front line treatments in a number of cancer types, with additional FDA approvals pending. Although personalized medicine has dominated the therapeutic field for quite a while, it is now becoming evident that mutation driven drug development is highly complex. Immuno therapies in particular utilize the body's own defense systems to target and kill cancer cells. Such therapies have researchers believing even more strongly now that a cure is possible. While metabolomics had a small presence, it is clear that a shift toward more global therapies is gaining in popularity again. Metabolomics is expected to play an important role, as cancer cells frequently have globally altered metabolic pathways as a means to drive proliferation.

Featured Articles

Metabolic parameters are calculated based on the concentration of metabolites involved in primary metabolic pathways. Each parameter reflects the specific activity of enzymes or metabolic pathways, and further their combination can provide a comprehensive assessment of the intracellular or extracellular status of metabolism.
Our primary service CARCINOSCOPE provides the absolute concentration of 116 metabolites together with 30 major metabolic parameters, and supports the understanding of metabolic changes engaged in human diseases, including cancer. Here, we introduce recent studies utilizing these metabolic parameters.

Adenylate Energy Ratio

Metabolomic alterations in human cancer cells by vitamin C-induced oxidative stress
Megumi Uetaki *et al.*, *Sci. Rep.*, 5: 13896, 2015

Intravenous administration of high-dose vitamin C has recently attracted attention as a cancer therapy. High-dose vitamin C induces pro-oxidant effects and selectively kills cancer cells. However, the anticancer mechanisms of vitamin C are not fully understood. Here, we analyzed metabolic changes induced by vitamin C in MCF7 human breast adenocarcinoma and HT29 human colon cancer cells using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS).

The roles of IP3 receptor in energy metabolic pathways and reactive oxygen species homeostasis revealed by metabolomic and biochemical studies
He Wen *et al.*, *Biochim. Biophys. Acta.*, 1853, pp. 2937-2944, 2015

Inositol 1,4,5-trisphosphate receptors (IP3Rs) are calcium channels modulating important calcium-mediated processes. Recent studies implicate IP3R in cell metabolism, but specific evidence is missing regarding IP3R's effects on actual metabolic pathways and key energy metabolites. Here, we applied metabolomics and molecular biology to compare DT40 cell lines devoid of IP3R (KO) and its wild-type (WT) counterpart.

Lactate / Pyruvate Ratio

13C-MR Spectroscopic Imaging with Hyperpolarized [1-13C]pyruvate Detects Early Response to Radiotherapy in SCC Tumors and HT-29 Tumors
Keita Saito *et al.*, *Clin. Cancer Res.*, in press, 2015

X-ray irradiation of tumors causes diverse effects on the tumor microenvironment, including metabolism. Recent developments of hyperpolarized 13C-MRI enabled detecting metabolic changes in tumors using a tracer [1-13C]pyruvate, which participates in important bioenergetic processes that are altered in cancers. Here, we investigated the effects of X-ray irradiation on pyruvate metabolism in squamous cell carcinoma (SCCVII) and colon cancer (HT-29) using hyperpolarized 13C-MRI.

Therapeutic Targeting of the Warburg Effect in Pancreatic Cancer Relies on an Absence of p53 Function
N.V. Rajeshkumar *et al.*, *Cancer Res.* 75, pp. 3355-3364, 2015

The "Warburg effect" describes a peculiar metabolic feature of many solid tumors, namely their increased glucose uptake and high glycolytic rates, which allow cancer cells to accumulate building blocks for the biosynthesis of macromolecules. During aerobic glycolysis, pyruvate is preferentially metabolized to lactate by the enzyme lactate dehydrogenase-A (LDH-A), suggesting a possible vulnerability at this target for small-molecule inhibition in cancer cells. In this study, we used FX11, a small-molecule inhibitor of LDH-A, to investigate this possible vulnerability in a panel of 15 patient-derived mouse xenograft (PDX) models of pancreatic cancer.

SAM/SAH Ratio

Histone Methylation Dynamics and Gene Regulation Occur through the Sensing of One-Carbon Metabolism

Samantha J. Mentch *et al., Cell Metab,* 22, pp. 861-873, 2015

S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) link one-carbon metabolism to methylation status. However, it is unknown whether regulation of SAM and SAH by nutrient availability can be directly sensed to alter the kinetics of key histone methylation marks. We provide evidence that the status of methionine metabolism is sufficient to determine levels of histone methylation by modulating SAM and SAH.

Recent Publications

Hepatocyte β-Klotho regulates lipid homeostasis but not body weight in mice

Kanako Kobayashi *et al., The FASEB Journal,* in press, 2015

β-Klotho (β-Kl), a transmembrane protein expressed in the liver, pancreas, adipose tissues, and brain, is essential for feedback suppression of hepatic bile acid synthesis. Because bile acid is a key regulator of lipid and energy metabolism, we hypothesized potential and tissue-specific roles of β-Kl in regulating plasma lipid levels and body weight. By crossing β-kl-/- mice with newly developed hepatocyte-specific β-kl transgenic (Tg) mice, we generated mice expressing β-kl solely in hepatocytes (β-kl-/-/Tg). Gene expression, metabolomic, and in vivo flux analyses consistently revealed that plasma level of cholesterol, which is over-excreted into feces as bile acids in β-kl-/-, is maintained in β-kl-/- mice by enhanced de novo cholesterogenesis.

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