HMT Newsletter

Friends and Colleagues,

Welcome to the July issue of our newsletter. This issue will focus on "Understanding Cancer Metabolism: the HMT way".

Metabolic reprogramming in cancer cells has been recognized as one of the most significant hallmarks of cancer. Cancer cells rewire their metabolism and energy production pathways to support and enable rapid growth, metastasis, drug resistance and survival.
Some of the most significant changes of tumor bioenergetics include increases in glycolysis, glutaminolytic flux, amino acid and lipid metabolism, mitochondrial biogenesis, pentose phosphate oxidative or reductive pathways and macromolecule biosynthesis.

At HMT, one of our primary goals is to provide cancer researchers with an under the hood, comprehensive quantitative assessment and pathway interpretation of cancer metabolism and metabolic flux. This month's articles and interview with Dr. Kensuke Tateishi exemplify this commitment we have to understanding cancer metabolism.

Sincerely,

Alexander Buko, PhD
Vice President
Human Metabolome Technologies America

HMT special interview

Dr. Kensuke Tateishi
Massachusetts General Hospital

On April 13th, Dr. Tateishi, a researcher at Massachusetts General Hospital, published the article titled "Myc-driven glycolysis is a therapeutic target in glioblastoma" in *Clinical Cancer Research*. In this article, he employed our metabolic profiling analysis to reveal that mutation-specific metabolic imbalances can be used as novel therapeutic targets. We asked Dr. Tateishi about his approach to the development of cancer therapy and the value of metabolic profiling for that purpose.

***HMT*: In the recent publication, you wrote about metabolic dysfunction caused by *C-Myc* mutations. What is new in this area?**

Dr. Tateishi: Although the *MYC* oncogene is frequently deregulated in human cancer, neither its involvement in the pathogenesis of glioblastoma, nor an effective treatment has been established. We recently revealed that a deregulated *MYC* resulted in over-activation of signal transduction, increasing the metabolic dependency of the tumor on glycolysis for the production of ATP.

Moreover, it increased the requirement for nicotinamide (NAD). We then uncovered that the inhibition of NAD biosynthesis effectively suppressed tumor growth *in vitro* and *in vivo*. These metabolic changes were restored by *c-Myc* and *n-Myc* shRNA. This NAD dependency is considered a specific phenotype of the deregulated *MYC* subtype. We have confirmed these metabolic changes and growth inhibition using specific inhibitors in patient derived cancer stem cells. These results support the hypothesis that NAD metabolism is a potential new target for the treatment of patients with deregulated *MYC*.

HMT: **How did you get started using HMT's metabolomic platform?**

Dr. Tateishi: In this study, we needed to determine the direction of metabolic changes and rate-limiting points in *Myc* induced metabolic pathways. Before using metabolomic profiling, we measured single intermediates in the glycolytic pathway (*e.g.* DHAP) and confirmed blocking NAD synthesis inhibited glycolysis. However, the data was a bit weak to conclude the direction or consequence of the metabolic changes. Reviewers suggested we needed more detailed pathway data to understand metabolic vulnerability in *MYC* deregulated cells. By using HMT's comprehensive quantitative metabolic profiling, together with 13C labeling, we definitely demonstrated that glycolysis was activated in *MYC* deregulated cells and subsequently decreased by the inhibition of NAD synthesis. Furthermore, we confirmed the decreased ATP by NAD depletion, which was a critical piece of data that explained the cellular growth suppression.

HMT: **What were the benefits of HMT's metabolomics for your studies?**

Dr. Tateishi: Our lab has a potential to use a variety of bioanalysis tools, such as genetic analysis, but a metabolite profile can give us more direct and specific information about changes in metabolomic activities. Because metabolite expression reflects intracellular changes closer to the phenotype than gene or protein expression, it can provide us intuitive and specific descriptions about tumor pathway activities. In this work, HMT provided a highly sensitive and quantitative analysis, which enables the comprehensive detection of many intermediates in glycolysis and central energy metabolism. In addition, HMT provided valuable discussions regarding the biological interpretation of our results. This was especially important for 13C labeling analysis, because we were unfamiliar with this approach. Lastly, their rapid response was greatly helpful to address concerns from reviewers.

HMT: **What is the future of your research?**

Dr. Tateishi: I am a Japanese neurosurgical scientist. I believe our research could lead to the development of new therapeutic opportunities for cancer patients. Our group has established protocols to culture stem cells from patient clinical samples, which enables us to reproduce the genotype and phenotype observed in cancer patients. A big advantage we have is the ability to determine gene mutations associated with specific metabolic imbalances as novel therapeutic targets. Regarding NAD, NAD depletion induces cellular death in some cancer genotypes. This approach is expected to provide novel therapeutic efficacy in tumor cells without cytotoxic effects in normal tissue. I plan to continue this research forward, working towards a clinical study. In addition to NAD targeted treatments for GBM, I want to pursue a better understanding of how mutations effect specific cancer metabolic pathways and contribute to the development of treatments to help cancer patients.

HMT: **Thank you for your time today. We look forward to our continued work together.**

Dr. Tateishi: You are welcome. I am pleased to share our research with your clients and collaborators.

- We appreciate Dr. Tateishi for sharing his project background and also the experience of our solution. HMT is happy to introduce applications from advanced researches of our clients. Please feel free to contact us if you are interested in on-site seminars.

References

1) Myc-driven glycolysis is a therapeutic target in glioblastoma. *Clin Cancer Res.* 2016 Apr 13.

Kensuke Tateishi, M.D., Ph.D.

Dr Tateishi earned his PhD in Yokohama City University and worked at MGH as a Postdoctoral Fellow from 2013 to 2016. He will return to Japan to work as a clinical physician and continue his research on brain tumors.

Featured articles

PHGDH Expression is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance and Lung Metastasis.

Samanta D., *et al., Cancer Res., in press.*

Intratumoral hypoxia stimulates enrichment of breast cancer stem cells (BCSCs), which are critical for metastasis and patient mortality. Here we report a metabolic adaptation that is required for hypoxia-induced BCSC enrichment and metastasis. Hypoxia-inducible factors coordinately regulate expression of genes encoding phosphoglycerate dehydrogenase (PHGDH) and five downstream enzymes in the serine synthesis pathway and mitochondrial one-carbon (folate) cycle.

Differential Glutamate Metabolism in Proliferating and Quiescent Mammary Epithelial Cells.

Coloff JL., *et al., Cell Metab.* **23**, *pp.* 867-880.

Mammary epithelial cells transition between periods of proliferation and quiescence during development, menstrual cycles, and pregnancy, and as a result of oncogenic transformation. Utilizing an organotypic 3D tissue culture model coupled with quantitative metabolomics and proteomics, we identified significant differences in glutamate utilization between proliferating and quiescent cells.

Spheroid cancer stem cells display reprogrammed metabolism and obtain energy by actively running the tricarboxylic acid (TCA) cycle.

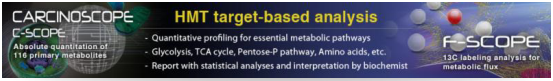
Sato M., *et al., Oncotarget, in press.*

The Warburg effect is a metabolic hallmark of cancer cells; cancer cells, unlike normal cells, exclusively activate glycolysis, even in the presence of enough oxygen. On the other hand, intratumoral heterogeneity is currently of interest in cancer research, including that involving cancer stem cells (CSCs). In the present study, we attempted to gain an understanding of metabolism in CSCs that is distinct from that in non-CSCs.

Glycolytic pathway affects differentiation of human monocytes to regulatory macrophages.

Suzuki H., *et al., Imm. Letters,* **176**, *pp.* 18-27.

Cellular metabolic state and individual metabolites have been reported to regulate the functional phenotype of immune cells. Cytokine production by regulatory and inflammatory macrophages is thought to mainly involve fatty acid oxidation and glycolysis, respectively, which fuel mitochondrial oxidative phosphorylation. However, the association between metabolic pathways and the acquisition of specific macrophage phenotypes remains unclear. This study assessed the relationship between glycolysis and the differentiation of regulatory macrophages.



HMT is a leading company providing metabolomic profiling based on unique and high performance CE-MS technology. We complete over 400 projects a year and our technology has contributed to the advancement of research in a variety of scientific areas.

Edited by Takushi Oga, PhD

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