October 2016

HMT Newsletter

Friends and Colleagues,

Metabolomic profiling is far from a one trick pony. It has long been established that the knowledge gained from metabolomic profiling and measurements cut across virtually all disciplines (food, beverage, agriculture, nutritionals, pharmaceutical, biotechnology and more) providing critical data for both basic and applied research.
This month's newsletter demonstrates HMT's commitment to support metabolomics covering such a variety of fields of study from ischemic heart disease metabolism, to influences of diet on *R. Philippinarum* (saltwater clams), to amino acid metabolism in supragingival (dental) plaques, to 3D cancer cell cultures. Precise, accurate and sensitive metabolite measurements using specimen specific extraction protocols allows us to measure and report critical metabolite pathways for our clients.

I would like to thank Dr. Jonathan Coloff from Harvard Medical School for this month's client testimonial. Dr. Coloff is pioneering the use of 3D tissue cultures to study cancer proliferation. He is working out the challenges and outcomes of this work to advance the field of cancer metabolism and cancer therapy. HTM is proud to be part of his research program bringing new directions to cancer metabolism.

Sincerely,

Alexander Buko, PhD
Vice President
Human Metabolome Technologies America

Collaborator spotlight

A New Dimension of Cancer Metabolism

Dr. Jonathan Coloff
Department of Cellular Biology
Harvard Medical School

The last 15 years have brought an expansion of interest in understanding the unique metabolic features of cancer cells, with an eye towards the ultimate goal of targeting cancer metabolism for therapy. But as with all aspects of cancer biology, our knowledge of cancer metabolism is only as good as the model systems that we utilize. Most studies of cancer metabolism have been performed on cancer cell lines grown in traditional tissue culture systems. When combined with metabolomics and stable isotope tracing methods, these systems can yield tremendously detailed information about cellular metabolism, including measurements of intracellular metabolic reaction rates (*i.e.*, metabolic fluxes).

These types of studies have contributed to an impressively large and continually expanding base of knowledge about how cancer cells utilize nutrients to meet the biosynthetic demands of rapid proliferation and to survive in harsh environments. However, as is the case with all cancer biology research, it is important to validate findings from cultured cells in *in vivo* models. And while significant progress has been made, studying metabolism in vivo remains challenging. This is especially true for studies that make use of stable-isotope tracing methods, largely due to the systemic effects of metabolically active tissues like muscle and the liver, which make the acquisition of tumor cell-autonomous data challenging.

In numerous sub-disciplines of cancer biology, three-dimensional (3D) tissue culture models have provided a valuable middle ground between traditional 2D tissue culture and *in vivo* methods. These culture systems, which typically involve the addition of reconstituted extracellular matrix (ECM) proteins (*e.g.*, Matrigel) to cell cultures, provide cells with a more physiological environment that more accurately preserves the cell-cell and cell-matrix interactions that are important regulators of cellular behavior *in vivo*. Importantly, interaction with ECM has also been shown to regulate normal and cancer cell metabolism, thereby placing a premium on utilizing culture systems in which these interactions are maintained. Of course, studying metabolism in 3D isn't without its own set of challenges, including generating sufficient cellular material for metabolomics and developing methods of rapidly harvesting metabolites away from excess ECM protein. As these hurdles are overcome, 3D systems that maintain the benefits of 2D tissue culture (*e.g.*, ease of genetic manipulation, fast experiments) while preserving critical aspects of the *in vivo* microenvironment will complement existing models and provide significant benefits to the cancer metabolism field.

Meeting the challenges of the expanding field of cancer metabolism will require a full arsenal of model systems, including 2D, 3D, organoid, *in vivo*, and *ex vivo* models, as each system has its advantages. Importantly, all studies of cancer metabolism, regardless of the model system used, rely on accurate measurement of metabolite levels. That's why it is important to have a system in place where one can be confident in the technical measurements, allowing researchers to focus on solving the biological questions that we face while exploring cancer metabolism as a potential therapeutic vulnerability.

Reference
Differential Glutamate Metabolism in Proliferating and Quiescent Mammary Epithelial Cells. *Cell Metabolism*, **23**, *pp*. 867-880, 2016.

Biography:

Dr. Coloff grew up in Iowa and attended Iowa State University for his undergraduate work. He earned his PhD from Duke University, where he studied interactions between metabolism and cell death in Dr. Jeff Rathmell's lab. For his postdoctoral work, he has studied tumor metabolism in Dr. Joan Brugge's lab at Harvard Medical School, focusing on the contribution of proliferation to the cancer metabolic phenotype.

Featured articles

Visualization of in vivo metabolic flows reveals accelerated utilization of glucose and lactate in penumbra of ischemic heart.

Sugiura Y. *et al., Sci. Reports*, **6**: 32361.

Acute ischemia produces dynamic changes in labile metabolites. To capture snapshots of such acute metabolic changes, we utilized focused microwave treatment to fix metabolic flow *in vivo* in hearts of mice 10 min after ligation of the left anterior descending artery. The left ventricle was subdivided into short-axis serial slices and the metabolites were analyzed by capillary electrophoresis mass spectrometry and matrix-assisted laser desorption/ionization imaging mass spectrometry. These techniques allowed us to determine the fate of exogenously administered (13)C6-glucose and (13)C3-lactate.

A metabolic profile in Ruditapes philippinarum associated with growth-promoting effects of alginate hydrolysates.

Yamasaki Y. *et al., Sci. Reports*, **6**: 32829.

The aim of this study is to demonstrate the growth-promoting effect of alginate hydrolysates (AHs) on the Manila clam Ruditapes philippinarum, and to verify the physiological change occurring within a living R. philippinarum stimulated by AHs. We show that growth of clams was dramatically promoted by supplementing a diet of the diatom Chaetoceros neogracile with AHs at 4 mg/mL. Furthermore, metabolomics indicates that each state of starvation, food satiation, and sexual maturation have a characteristic pattern.

Amino acid composition and amino acid-metabolic network in supragingival plaque.

Washio J. *et al., Biomed. Res.*, **37**, *pp*. 251-257.

Dental plaque metabolizes both carbohydrates and amino acids. The former can be degraded to acids mainly, while the latter can be degraded to various metabolites, including ammonia, acids and amines, and associated with acid-neutralization, oral malodor and tissue inflammation. However, amino acid metabolism in dental plaque is still unclear. This study aimed to elucidate what kinds of amino acids are available as metabolic substrates and how the amino acids are metabolized in supragingival plaque, by a metabolome analysis.

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