January 2018

HMT Newsletter

Friends and Colleagues,

Welcome to the new year and new opportunities,

We at HMT Boston have had a chilly and snowy start to 2018. Despite the weather, we are here to discuss with you or your colleagues' new opportunities and to work with you on your research goals. We are looking forward to sharing with you our new offerings this year as well, so stay tuned for future announcements.

Sincerely,

Alexander Buko, PhD
Vice President
Human Metabolome Technologies America

A New Year's Gift

Now, with all projects in January and February, receive an iPad!

Find Out More

C-SCOPE - Understanding cancer metabolism through central carbon pathways

What Does C-SCOPE tell you about cancer cells and cancerous tissue?

C-SCOPE is a targeted quantitative CE-MS method that generates the concentration of over 100 metabolites in cell extracts or tissue samples that relate information on;

- Energy status: ATP, ADP, AMP, NADH, NAD, NADP+
- Biomass synthesis or catabolism; (Purines, pyrimidines, fatty acids, amino acids, lipid regulating metabolites; (DHAP, Glycerol3-phosphate, citrate)
- Salvage pathways (nucleic acids, amino acids, pentose phosphate pathway)
- Nutrient status / glucose consumption; (glycolytic intermediates, TCA cycle, amino acids)

Cancer cells through the glycolytic pathway and mitochondria adapt in their own microenvironment and in a treatment environment to survive. C-SCOPE tells us how this landscape changes in tumors when cancer cells take over, how it changes with a growing tumor and how it reacts to therapeutic treatment.

Tumors are known for their cellular / genetic diversity - adaptation to change. Different tumor types (Bladder, Kidney, Colon, Lung, Pancreas, Breast) present a different glycolytic environment hence display unique profiles uniting genetic diversity within the tumor with the nutrient availability within the tissue micro-environment. Different tissues present different metabolic nutrient compositions (fats, protein, lipids, nucleic acids) and different ways to process these metabolites.

C-SCOPE provides a key to understanding and unraveling these complex processes.

Featured articles

ADHFE1 is a breast cancer oncogene and induces metabolic reprogramming

Mishra, P., et al., J Clin Invest. 2018;128(1):323-340.

Key Points:

- Previous data shows D-2HG production in breast cancer not related to IDH mutations
- Presence of D-2HG is inversely related to patient survival
- The D-2HG-producing mitochondrial enzyme, alcohol dehydrogenase, iron-containing protein 1 (ADHFE1), is a breast cancer oncogene
- MYC upregulates ADHFE1 leading to metabolic changes related to reactive oxygen and reductive glutaminolysis resulting in cellular dedifferentiation, enhanced mesenchymal transition, and phenocopying alterations that occur with high D-2HG levels in cancer cells with IDH mutatations

Lovastatin induced Kruppel like factor 2 (KLF2), Kruppel like factor 6 (KLF6) and Ras homolog family member B (RHOB) genes and preferentially led to viability reduction of Cisplatin-resistant cells

Koi C., *et al.*, *Oncotarget*. 2017 Dec 5; 8(63): 106429-106442.

Key Points:

- It has been previously reported that statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase that are used to prevent hypercholesterolemia, have antitumor activity in several cancers
- In this study, cisplatin resistant cell lines were shown to possess high sensitivity to Lovastatin compared to their parental cell lines
- The genes KLF2, KLF6, and RHOB were found to be upregulated by statin treatement
- It has been reported that KLF2 and KLF6 act as tumor suppressor genes, and downregulation of KLF2 or KLF6 was associated with poor survival in several cancers
- RHOB is one of the Rho family of small GTPases, signaling molecules that regulate many cellular processes including cytoskeletal dynamics, cell motility, cell adhesion, cell division, and transcription
- These results suggest that statins might have the potential to overcome Cisplatin resistance as single-agent therapy

Mutations of the Glycine Cleavage System Genes Possibly Affect the Negative Symptoms of Schizophrenia through Metabolomic Profile Changes

Yoshikawa, A., *et al.*, *Psychiatry Clin. Neurosci.*. Accepted Author Manuscript

Key Points:

- Hypofunction of N-methyl-D-aspartate receptors (NMDARs) may contribute to the pathophysiology of schizophrenia (SCZ)
- The glycine cleavage system (GCS) was shown to affect NMDAR function in the brain.
- After re-sequencing the GCS enzymes in 474 patients with SCZ, damaging variants were found in GLDC and AMT
- Metabolomic profiling in patients harboring GCS variants also revealed marked elevation of plasma 5-oxoproline (pyroglutamic acid), aspartate, and glutamate, which might affect NMDARs function

Edited by Laura Shelton, PhD

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