



# HMT Newsletter

Dear Researchers,

At Human Metabolome Technologies Inc. (HMT), we are constantly looking for new ways to improve our client satisfaction. I am pleased to announce our monthly HMT newsletter containing science updates, new product development and HMT related publications. In addition, for 2015 we have restructured our prices and reduced our minimum number of samples for our profiling services. Metabolomics is an emerging field and a necessary part of personalized medicine, basic research and drug development. Please let us know of your metabolomics needs or questions. We are looking forward to supporting your research.

Sincerely,

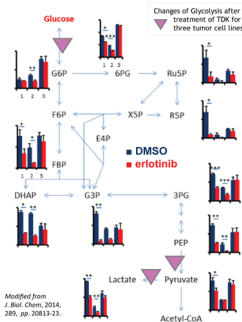
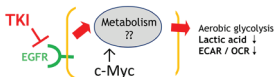
Tsutomu Hoshiba  
 President  
 Human Metabolome Technologies America

## Medical Research

### Epidermal Growth Factor Receptor (EGFR) Signaling Regulates Global Metabolic Pathways in EGFR-mutated Lung Adenocarcinoma.

Hideki Makinoshima *et al.*, *J. Biol. Chem.* 289, pp. 20813-23, 2014

Mutations in the tyrosine kinase epidermal growth factor receptor (EGFR) induce oncogenic addiction in lung adenocarcinoma (LAD). The study showed that EGFR signaling plays an important role in aerobic glycolysis in EGFR-mutated LAD cells. EGFR-tyrosine kinase inhibitors (TKIs) decreased lactate production, glucose consumption, and the glucose-induced extracellular acidification rate (ECAR). Metabolomic analysis revealed that metabolites in the glycolysis, pentose phosphate pathway (PPP), pyrimidine biosynthesis, and redox metabolism were significantly decreased after treatment of LAD cells with EGFR-TKI. We conclude that EGFR signaling regulates the global metabolic pathway in EGFR-mutated LAD cells. The data provide evidence that may link therapeutic response to the regulation of metabolism, which is an attractive target for the development of more effective targeted therapies.



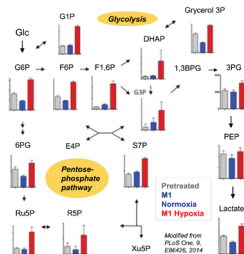
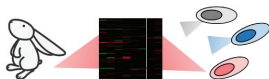
From the metabolomics, down-regulation in aerobic glycolysis induced by TKI treatment, which was confirmed by extracellular biochemical monitoring, was linked to inhibitions in up-stream metabolic pathways including the PPP, suggesting the existence of target enzymes involved in glucose incorporation. As hypothesized, MYC-dependent regulation of glucose intake was modulated as a result of inhibition by EGFR-TKI. Additionally, glutaminolysis, de novo DNA synthesis, and glutathione turn over was also modulated by EGFR-TKI inhibition.

## Medical Research

### Increased Metabolite Levels of Glycolysis and Pentose Phosphate Pathway in Rabbit Atherosclerotic Arteries and Hypoxic Macrophage.

Atsushi Yamashita *et al.*, *PLoS One*, 9, e86426, 2014

Inflammation is considered to affect glucose utilization in atherosclerotic arteries. The authors identified metabolic changes engaged in glucose uptake and hypoxia in rabbit atherosclerotic arteries and macrophages. Macrophage-rich or smooth muscle cell (SMC)-rich neointima was created by balloon injury. Macrophages stimulated with lipopolysaccharides (LPS), and interferon- $\gamma$  (INF $\gamma$ ) were cultured under normoxic and hypoxic conditions. The levels of glycolytic and pentose phosphate pathway metabolites increased in LPS and INF $\gamma$  stimulated macrophages under hypoxic but not normoxic condition. The data showed that infiltrative macrophages might affect metabolic systems, and hypoxia but not classical activation might augment glycolytic and pentose phosphate pathways in macrophages.



Changes in metabolites after activation of cultured macrophages.

From the metabolomics, activation of glucose metabolism was accompanied by a wide range of metabolic transformations such as aerobic glucose consumption, nucleotide and protein turn-over, and glutathione metabolism under hypoxic conditions of activated macrophage cells. The data suggests that not only macrophage activation, but also hypoxic environments are key factors contributing to increased glucose intake which is observed in atherosclerotic arteries in the rabbit model.



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