HMT Newsletter

Dear Researchers,

Welcome to the August issue of the HMT newsletter. We hope you are enjoying the sunshine and making the most of summer.

In this month's newsletter, Dr. Thomas Seyfried, Professor of Biology at Boston College, has written an article for us about his research about cancer being a mitochondrial metabolic disease. He is the author of the well-regarded book 'Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer' (ISBN-10: 0470584920) and a longtime friend of HMT.

Dr. Seyfrieds' study of cancer metabolism addresses controversies related to the origins of cancer and provides solutions to cancer management and prevention. He expands upon Otto Warburg's well-known theory that all cancer is a disease of energy metabolism. This is very important work and we are pleased to share some of his ideas with you.

Sincerely,

Tsutomu Hoshiba
CEO
Human Metabolome Technologies America

Collaborator Spotlight

HMT takes great pride in working with some of the most prestigious researchers in the world, dedicating our technologies to help advance their research. This month we are featuring Dr. Thomas Seyfried of Boston College.

Dr. Seyfried has been a researcher and professor at Boston College for 30 years with over 150 publications and many honors. His work has focused extensively on liposomal storage disorders and recently cancer metabolism. Dr. Seyfried has researched and published at length on the therapeutic potential of calorie restriction and ketogenic diets for the metabolic management of cancer. His work and that of others will pave the way for novel non-toxic, highly effective cancer treatments.

We have asked Dr. Seyfried to share some of his thoughts on how metabolomics can lead to a better understanding of cancer and to novel therapeutic targets.

Targeting tumor cell fermentation for cancer management

Thomas N. Seyfried, Ph.D.
Boston College

Emerging evidence indicates that cancer is a mitochondrial metabolic disease according to the original theory of Otto Warburg. Abnormalities in the number, structure, or function of mitochondria in tumor cells leads to a metabolic shift in energy production from oxidative phosphorylation (respiration) to substrate level phosphorylation (fermentation). The Warburg Effect (aerobic fermentation of lactate) is a common metabolic phenotype seen in the majority of cancers and arises as a direct consequence of abnormalities in tumor cell mitochondria. The vast numbers of gene defects seen in tumor cells arise as downstream effects of this shift in energy production and are considered "red herrings" in our quest to understand and manage cancer. Many oncogenes are transcription factors that drive metabolic pathways for fermentation following defects in mitochondrial respiration. Oncogene targeting, however, is limited as an effective therapeutic strategy for cancer management due pathway redundancies. On the other hand, limitation of fermentable fuels offers a more realistic strategy for cancer management. Glucose is the prime fuel for tumor energy production and growth. Lactate is produced as the major waste product of glucose fermentation through the Embden-Myerhoff-Parnas glycolytic pathway. Therapies that limit glucose availability to tumor cells will reduce lactate production and consequently energy production and growth. In addition to aerobic glucose fermentation, tumor cells can also ferment some amino acids. Amino acid fermentation can aid in tumor cell survival and growth especially under hypoxic conditions that exist in many solid tumors. Waste products of amino acid fermentation can include glutamate, alanine, succinate, acetate, and ammonia.

Metabolomics can help identify the fermentable fuels that tumor cells use for their growth and survival through analysis of the waste products. It should be recognized that secondary waste products could also be produced from the primary fermentation waste products. Identification of key fermentable fuels for tumor cells can occur through analysis of both primary and secondary waste products. It will therefore be necessary to compare the signature of energy fuel waste metabolites of tumor tissue with those from normal tissue. Waste metabolite analysis can also be evaluated in cultured tumor cells that are fed with various glucose and amino acid combinations. It is important to recognize, however, that the Crabtree effect can confound data interpretation from cultured cells. The Crabtree effect arises from the suppression of respiration from glucose in the culture media. It therefore becomes difficult to determine whether fermentation waste products seen in vitro arise as an artifact from suppressed respiration (Crabtree effect) or arise from abnormal mitochondrial function (Warburg effect). Appropriate non-tumor cell control groups grown in the presence or absence of glucose can be used to help distinguish metabolic waste products arising from either the Crabtree or the Warburg effects. As mitochondrial defects prevent tumor cells from effectively using ketone bodies (acetoacetate and β-hydroxybutyrate) for energy, ketogenic diets can be used to target energy metabolism in tumor cells. This therapeutic strategy is receiving increased attention as a non-toxic approach for managing a broad range of cancers that rely on glucose for energy and growth. Calorie restricted ketogenic diets will reduce lactate production and could also alter the metabolic signature of amino acid fermentation. Hence, metabolomic analyses that profile tumor cell energy metabolites arising from glucose and amino acid fermentation will help to identify those fuels that can be targeted for managing cancer.

Further Reading

Seyfried TN, Flores R, Poff AM, D'Agostino DP. Cancer as a Metabolic Disease: Implications for Novel Therapeutics.
Carcinogenesis. 35: 515-527, 2014.

Poff AM, Ari C, Arnold P, **Seyfried TN**, D'Agostino DP. Ketone supplementation decreases tumor cell viability and prolongs survival of mice with metastatic cancer.
Int J Cancer. 2014 Oct 1;135(7):1711-20. doi: 10.1002/ijc.28809.

Human Metabolome Technologies America
24 Denby Road, Suite 217, Boston, MA 02134, USA | p. 617-987-0554 | f. 617-902-2434
hmtamerica@humanmetabolome.com I humanmetabolome.com/en