BeNeLux METABOLOMICS centre

Online Benelux Metabolomics Seminar on

Thursday
27 November
15:30-17:00

"One-carbon metabolism in cancer."

Nathalie Legrave

Johannes Meiser

Kim Eiden

Programme

15:30 Introduction
Nathalie Legrave, Luxembourg Institute of Health, Luxembourg, Luxembourg

15:35 Functions of Formate in Cancer
Johannes Meiser, Cancer Metabolism Group, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg

16:25 Metabolomics as a tool to elucidate metabolic vulnerabilities of cancer cells and explore them for cancer therapy
Kim Eiden, Cancer Metabolism Group, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg

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Register here

Abstracts

Functions of Formate in Cancer

Johannes Meiser
Cancer Metabolism Group, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg.

Abstract
The metabolic landscape of the tumor microenvironment can have profound impact on disease progression. Nutrient availability but also release of different metabolites from stromal and cancer cells can affect cancer cell behavior as well as immune cell functionality.
A prime example for such plastic metabolism is the amino acid serine. Others and we have demonstrated that the rate and fate of serine metabolism can change according to cellular state. In particular, we have uncovered that the rate of serine catabolism often exceeds the anabolic demand of cancer cells, resulting in formate overflow. Elevated formate concentrations in the extracellular space promote metastasis in a growth-independent manner. More recently, several lines of evidence indicate that formate acts as a double edged sword by either promoting metastasis or supporting immune-checkpoint therapy by boosting T-Cell function.
Here, I will discuss the different roles of formate and present an additional cancer cell intrinsic aspect driven by elevated formate concentrations.

Metabolomics as a tool to elucidate metabolic vulnerabilities of cancer cells and explore them for cancer therapy

Kim Eiden
Cancer Metabolism Group, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg.

Metabolic reprogramming is a hallmark of cancer and reflects the ability of tumor cells to adapt to fluctuating nutrient and signalling environments. Metabolomics provides comprehensive analysis of metabolites within cells, tissues, or biofluids and has emerged as a powerful approach to uncover these dynamic changes. High-resolution mass spectrometry combined with stable isotope tracing enable a precise mapping of metabolic fluxes within tumor cells and provides an integrated view of the biochemical alterations that drive cancer initiation, progression, and therapeutic resistance.
The core interest of our research group is the one-carbon metabolism (OCM), an essential metabolic pathway for nucleotide biosynthesis and sustained cellular redox balance. The mitochondrial OCM enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) is frequently upregulated in tumors but absent in most adult tissues, making it an attractive therapeutic target. Hence, we applied metabolomics to dissect the metabolic consequences of pharmacological and genetic perturbation of the OCM in cancer cells. Using selective small-molecule inhibitors (TH9619, TH9975) and CRISPR/Cas9-mediated MTHFD2 knockout, we observed a pronounced depletion of purine and pyrimidine nucleotides. Stable isotope tracing further revealed disrupted dTMP and purine biosynthetic fluxes, accompanied by accumulation of folate intermediates translating into a toxic folate trapping. Furthermore, we uncovered metabolic adaptation mechanisms upon purine depletion in cancer cells which potentially supports the persistence of these cells and their dissemination across other organs which we refer to as metastasis.
Overall, metabolomics offers unique opportunities to uncover vulnerabilities in cancer metabolism and accelerate the development of targeted clinical strategies.