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Using stable isotope resolved metabolomics to characterize glycolytic inhibition and to decode synthetic lethality in cancer

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Metabolic reprogramming is a key step in oncogenic transformation including the activation of energy and anabolic metabolism. The central metabolism is the ultimate source of energy and building blocks enabling growth and proliferation. Specifically, time-resolved analysis of central metabolic pathways is needed for a better understanding of metabolic dynamics and the comparison and even quantification of pathway usage. In order to quantify the usage and activity of central metabolic pathways we have developed pulsed stable isotope resolved metabolomics (pSIRM) to analyse metabolism *in vitro* and *in vivo*. The applied GC-MS based technology enables the absolute quantification of metabolites and at the same time the determination of stable isotope incorporation, thus it allows also quantifying metabolic dynamics *in vivo*. Since the observation that glycolysis is deregulated in cancer the central metabolism gained attention as a possible therapeutic target. We have characterized the action of glycolytic inhibitors using pSIRM in a time dependent manner to distinguish between actual metabolic inhibition and adaptive processes. We observed unexpected effects and argue that the commonly used compound 2-deoxyglucose is not a specific glycolytic inhibitor. In order to understand the metabolic vulnerabilities at a molecular level we together with our co-workers have investigated the metabolic aspect of synthetic lethal interaction around the oncogene cMyc and could uncover metabolic circuits in regulatory networks that may open new ways for combinatorial therapies including metabolic inhibition.

Biography

Stefan Kempa has completed his PhD at the University of Potsdam and performed his Postdoctoral studies at the IMBA/GMI in Vienna focusing on the crosstalk between signaling and metabolism in plants. He is leading a Research and Technology Group at the Berlin Institute for Medical Systems Biology-Max Delbruck Center in Berlin, Germany.

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