Using natural yeast isolates to understand the function of an orphan metabolite

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2-Hydroxyglutarate (2HG) is an atypical metabolite that accumulates in neurometabolic diseases as well as in certain types of cancer. The mechanisms through which 2HG leads to cell transformation or neurodegeneration remain, however, poorly understood. Compared to the research on 2HG in mammalian systems, and despite certain advantages of yeast as a model organism for biomedical research, only a very limited number of studies reported on the occurrence and metabolism of 2HG in yeast. An extensive study performed over the last three years in our lab, revealed a panoply of new findings on 2HG metabolism of Saccharomyces cerevisiae. Among those the fact that the yeast phosphoglycerate dehydrogenases Ser3 and Ser33 convert α-ketoglutarate to D-2HG in addition to their primary metabolic role, which consists in catalysing the first step of the serine synthesis way converting 3-phosphoglycerate to 3-phosphohydroxypyruvate. Our results also show, however, that the two identified D-2HG producing enzymes do not represent the only sources of this metabolite in yeast Within our study, the two dehydrogenases Dld2 and Dld3 were both shown to convert D-2HG to α-ketoglutarate in vitro. Targeted metabolome analyses and biochemical characterisation led additionally to the original finding that DLD3 is actually an FAD-dependent trans-hydogenase that converts D-2HG to α-ketoglutarate, using pyruvate as a hydrogen acceptor. Based on our findings, we were for the first time able to propose a central carbon network of Saccharomyces cerevisiae integrating the metabolite D-2HG and connecting its metabolism to the mitochondrial respiratory chain. In the present research project we aimed to further elucidate the metabolic network involved in 2HG formation and degradation in yeast. Using targeted metabolome analysis and high-throughput growth phenotyping, we analysed the accumulation of D-2HG in genotyped natural yeast isolates. The analysis of strains carrying copy number variations of the gene DLD3 confirmed that it is the main regulator of 2HG, but also showed evidence for the presence of additional regulators.

Speaker Biography

Nicole Paczia obtained her doctorate from the University of Bielefeld (Germany) in 2012, and worked as a postdoctoral researcher at the Institute for Bio- and Geosciences 1 (Research center Jülich), before starting as a research associate at the Luxembourg centre for systems biomedicine (LCSB). In 2016, Dr. Paczia was awarded a CORE Junior Fellowship by the Luxembourg National Reseach Fund (FNR), which allowed her to establish a Junior Research group within the group for Enzymology and Metabolism, headed by Dr. Carole Linster at the LCSB. She has published more than 10 papers in reputed journals, and holds two patents.

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