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A novel metabolic feedback loop triggered by pyruvate kinase controls redox metabolism in respiring cells

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In proliferating cells, a transition from aerobic to anaerobic metabolism is known as the Warburg effect, whose reversal inhibits cancer cell proliferation. Studying the metabolic changes controllde by its regulator pyruvate kinase (PYK), we discovered that central metabolism is self-adapting to synchronize redox metabolism when respiration is activated.

We found that PYK activity activated yeast respiration. Surprisingly, levels of reactive oxygen species (ROS) did not increase, but cells gained resistance to oxidants. This adaptation was attributable to accumulation of the PYK substrate phosphoenolpyruvate (PEP). PEP acted as feedback inhibitor of the glycolytic enzyme triosephosphate isomerase (TPI). TPI inhibition stimulated the pentose phosphate pathway, increased anti-oxidative metabolism, and prevented ROS accumulation.

Thus, a metabolic feedback loop, initiated by PYK, mediated by its substrate and acting on TPI, synchronizes engergy- and redox metabolism when cells respire. Originating from a single catalytic step, this autonomous re-configuration of central carbon metabolism prevents oxidative stress upon shifts between fermentation and respiration.

Biography

M Ralser is Wellcome Trust fellow and completed his Ph.D in 2006 at the age of 26 years at the Max Planck Institute for Molecular Genetics (MPI-MG, Berlin). After Research experience at the University of Salzburg, the VU University of Amsterdam and the MPI-MG, he became Junior Group leader at the MPI-MG, and moved with his team to the University of Cambridge in 2011. He published more then 20 research papers as first or senior author, many in prestigious Journals including PNAS, Nature Biotechnology, Nature Protocols, Journal of Biology, Cell Metabolism & Science Signaling. He is associated editor of BMC Genomics, associated member of Faculty of 1000, and was awarded with the BioMed Central Research award 2007 and the Wellcome Beit Prize in 2010.