Molecular Systems Biology 7; Article number 478; doi:10.1038/msb.2011.10
Citation: ***Molecular Systems Biology*** **7:478**

www.molecularsystemsbiology.com

molecular systems biology

NEWS AND VIEWS

Transcriptional control of metabolic fluxes

Jens Nielsen*

Department of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden
* Corresponding author. Chemical and Biological Engineering, Chalmers University of Technology, Systems Biology, Gothenburg 41128, Sweden. Tel.: +46 31 772 3804; Fax: +46 31 772 3801; E-mail: nielsenj@chalmers.se
Molecular Systems Biology **7:** 478; published online 29 March 2011; doi:10.1038/msb.2011.10

Metabolism is at the core of cellular function, and it comprises thousands of reactions that are involved in the degradation of nutrients and biosynthesis of cellular constituents such as proteins, lipids, carbohydrates, DNA and RNA. These cellular constituents are macromolecules that are formed by polymerization of so-called building blocks. Key building blocks are amino acids (for biosynthesis of proteins), fatty acids (for biosynthesis of lipids), nucleotides (for biosynthesis of RNA and DNA), and sugar moieties (for biosynthesis of carbohydrates). While there are more than 50 building blocks, it is fascinating that these are all formed from only 12 so-called precursor metabolites (Nielsen, 2003). These 12 precursor metabolites are precursors for the formation of all organic chemicals found in nature, and hence the biosynthesis of these is remarkably conserved among all living organisms. They are formed from carbon and energy sources, e.g., glucose, fructose, and galactose, in what is generally referred to as the central carbon metabolism, which besides formation of the 12 precursor metabolites also ensures provision of Gibbs free energy, primarily in the form of ATP, and electron acceptors/donors, primarily in the form of NADH and NADPH, that are required for biosynthesis of building blocks and macromolecules. In order to ensure balanced provision of the 12 precursor metabolites, ATP, NADH, and NADPH for the many different metabolic functions required for the cell to survive in different environments, all organisms have evolved to have a very tight regulation of the central carbon metabolism.

Owing to the tight interaction of central carbon metabolism with overall cell function, there is much interest in gaining knowledge about its regulation. Such knowledge has both medical and industrial relevance. Along these lines, recent research has shown that there are large changes in the fluxes through the central carbon metabolism in connection with cancer development (Vander Heiden *et al*, 2009), and understanding the underlying regulation of these flux changes may allow for identification of novel treatment strategies. Also in the field of industrial biotechnology there is much interest in understanding how the central carbon metabolism in industrial microorganisms is regulated, as this may allow engineering of metabolism to redirect carbon fluxes toward precursors for industrially relevant metabolites (Keasling, 2010). However, due to lack of knowledge regarding the regulation of central carbon metabolism flux, it is often difficult to perform this kind of metabolic engineering.

In a recent, interesting article published in *Molecular Systems Biology*, Sauer and co-workers evaluate how different transcription factors control fluxes through the central carbon metabolism of the bacterium *Escherichia coli* (Haverkorn van Rijsewijk *et al*, 2011). Through the use of ^{13}C-labeled carbon sources, followed by measurement of the labeling in intracellular metabolites, they quantify the fluxes in the central carbon metabolism of *E. coli* grown on glucose or galactose. When comparing the fluxes on these two carbon sources, they found that with galactose there is primarily respiratory metabolism, whereas with glucose there is a substantial overflow metabolism toward acetate. What is interesting is that the respiratory metabolism on galactose does not solely involve the traditional tricarboxylic acid cycle, but also uses a combination of the glyoxylate cycle and phoshoenolpyruvate (PEP) carboxikinase for respiration. The use of this alternative respiratory pathway will require a relatively higher flux through pyruvate kinase, which can occur because PEP is not drained in connection with galactose uptake, as this sugar is not taken up by a phosphotransferase system (PTS). In PTS systems, used for glucose transport, the transport of the sugar is accompanied with sugar phosphorylation driven by the co-current conversion of PEP to pyruvate, and hence this transport system consumes PEP. For galactose this additional PEP may now be used for the slightly more energetically efficient glyoxylate–PEP carboxykinase respiration route (Fischer and Sauer, 2003).

Besides this interesting finding, the paper further provides new insight into the transcriptional regulation of the fluxes through the central carbon metabolism of *E. coli*. The authors quantified the metabolic fluxes in 91 mutants with deletions of individual transcription factors, on both glucose and galactose. On glucose, the authors do not find any large changes in the fluxes in any of the 91 mutants, except for some small re-direction of fluxes around the acetyl-CoA node, and none of the deletion mutants results in faster growth or increased glucose uptake rate. This is different from what is observed in

an earlier study on *Baccillus subtilis* in the same group (Fischer and Sauer, 2005), and it may indicate that *E. coli* has optimized its glucose uptake and growth on glucose to its maximum, whereas other organisms may have installed regulation to reduce the sugar uptake rate. For galactose the situation is, however, more similar to what has been found for *B. subtilis*. Here, deletion of five transcription factors results in improved galactose uptake and faster growth compared with the wild type. It is further shown that these transcription factors seem to regulate metabolism through the transcription factor, Crp, which is known to regulate metabolism directly, e.g., by increasing the transcription of PEP carboxykinase. Crp is a cAMP receptor protein that is activated by cAMP, whose level is decreasing with increasing glucose concentrations/uptake rates. To evaluate whether the flux through the glyoxylate cycle–PEP carboxykinase route is indeed repressed by glucose, the authors performed additional chemostat experiments, and they found that this route is functional at low glucose-uptake rates where the cAMP level is high. They further measured the concentration of cAMP in different mutants. On the basis of all these findings, it seems that galactose uptake and metabolism is repressed through Crp, and the repressor is most likely components of the glucose PTS.

Besides the fundamental insight into the regulation of fluxes in the central carbon metabolism in *E. coli*, the authors' work indicates that there is a fairly high degree of transcriptional regulation of metabolic fluxes in this bacterium. This has significant impact for the metabolic engineering of this organism to produce different chemicals. This finding may well hold for other bacteria, but it is surely not the case for eukaryal cells, e.g., the yeast *Saccharomyces cerevisiae*, where it is found that only a few reactions in the central carbon metabolism are transcriptionally regulated (Daran-Lapujade *et al*, 2007; Bordel *et al*, 2010).

Conflict of interest

The author declares that he has no conflict of interest.

References

Bordel S, Agren R, Nielsen J (2010) Sampling the solution space in genome-scale metabolic networks reveals transcriptional regulation in key enzymes. *PLoS Comput Biol* **6:** e1000859

Daran-Lapujade P, Rossell S, van Gullik WM, Luttik MA, de Groot MJ, Slijper M, Heck AJ, Daran JM, de Winde JH, Westerhoff HV, Pronk JT, Bakker BM (2007) The fluxes through glycolytic enzymes in *Saccharomyces cerevisiae* are predominantly regulated at post-transcriptional level. *Proc Natl Acad Sci USA* **104:** 15753–15758

Fischer E, Sauer U (2003) A novel metabolic cycle catalyzes glucose oxidation and anapleorosis in hungry *Escherichia coli*. *J Biol Chem* **278:** 46446–46451

Fischer E, Sauer U (2005) Large-scale *in vivo* flux analysis shows rigidity and suboptimal performance of *Bacillus subtilis* metabolism. *Nat Genet* **37:** 636–640

Haverkorn van Rijsewijk BRB, Nanchen A, Nallet S, Kleijn RJ, Sauer U (2011) Large-scale ^{13}C-flux analysis reveals distinct transcriptional control of respiratory and fermentative metabolism in *Escherichia coli*. *Mol Syst Biol* **7:** 477

Keasling JD (2010) Manufacturing molecules through metabolic engineering. *Science* **330:** 1355–1358

Nielsen J (2003) It is all about metabolic fluxes. *J Bacteriol* **185:** 7031–7035

Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: the metabolic requirement of cell proliferation. *Science* **324:** 1029–1033