

Abstract

Background: cDNA microarray studies result in a huge amount of expression data. The main focus lies often on revealing new components which end in long lists without understanding the global networks described by them. This doctoral thesis asks to which extent theoretical analyses can reveal gene networks, molecular mechanisms and new hypotheses in microarray expression data. For this purpose, gene expression profiles were generated using microarrays and a cell model for fat cell development.

Results: A novel adipogenic atlas was constructed using microarray expression data of fat cell development. In total, 659 gene products were subjected to *de novo* annotation and extensive literature curation. The resulting gene networks delineate phenotypic observations, such as clonal expansion, up-rounding of the cells and fat accumulation. Based on this global analysis, seven targets were selected for experimental follow up studies. Further, 26 transcription factors are suggested by promoter analysis to regulate co-expressed genes. 27 of 36 investigated pathways are preferentially controlled at rate-limiting enzymes on the transcriptional level. Additionally, the first set of 391 universal proteins that are known to be rate-determining was selected. This dataset was hand-curated from >15,000 PubMed abstracts and contains 126 rate-limiting proteins from curated databases with increased reliability. Two thirds of the rate-determining enzymes are oxidoreductases or transferases. The rate-limiting enzymes are dispersed throughout the metabolic network with the exception of citrate cycle. The knockout of the rate-limiting adipose triglyceride lipase responds in transcriptional down-regulation of the whole oxidative phosphorylation and specific control of many rate-limiting enzymes in brown fat tissue. Finally, it was shown that selective transcriptional regulation of rate-limiting enzymes is a widely applied mechanism for the control of metabolic networks.

Conclusion: This thesis demonstrates that large-scale transcription profiling in combination with sophisticated bioinformatics analyses can provide not only a list of novel players in a particular setting, but also a global view on biological processes and molecular networks.