Using pathway and network analysis to investigate the mechanisms in the diabetic liver

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Background: Type 2 Diabetes Mellitus is a vastly increasing health problem worldwide and obesity, the excess accumulation of lipids in the body, is a major risk factor for diabetes. It is well known that lipid accumulation in liver contributes to insulin resistance, hyperglycemia and hyperlipidemia. The hepatic lipid accumulation is the main characteristic of non-alcoholic fatty liver disease which is strongly associated with diabetes. A better understanding of the processes and regulatory mechanisms involved is needed to develop new interventions. In this study, a published transcriptomics dataset was analyzed using state-of-the art pathway and network analysis approaches to decipher the biological mechanisms in the liver of obese, diabetic patients with a fatty liver.

Methods: Pathway analysis was used to find significantly altered biological processes. Pathway databases like WikiPathways provide pathway collections commonly used in pathway analysis. Next, network analysis was applied to i) identify genes linking pathways related to diabetic liver, ii) investigate the transcriptional regulation within the pathways and iii) study the known drugs targeting genes in the pathways and their effects. The open-source and popular pathway and network visualization and analysis tools PathVisio and Cytoscape were used in this study.

Results: Pathway analysis revealed sixteen significantly altered pathways that were then combined in one biological network. Only one of the pathways is not connected to any of the others. Most of the nodes connecting the pathways in the network have important roles in energy metabolism and further analyses showed that transcription factors are regulating many genes in different pathways and therefore provide new links between them. The extension of the network with drug-targets confirmed several known antidiabetic drugs and allows the identification of other drugs targeting proteins up- or downstream that might interfere with the action or efficiency of a drug.

Conclusion: The approach described allows the combination and integration of information about disease affected pathways with knowledge on the involved genes and metabolites. TF regulation and drugs, as used in this study, are only examples of additional information that can be used. This leads to increased insight and clearer illustration of the overall process and allows researchers to define new research hypotheses. The systems biology approach demonstrated in this study is highly generic and can be applied in different research fields.