Abstract

MicroRNAs (miRNAs) regulate gene expression at the post-transcriptional level in most cell-biological processes. Deregulated miRNA expression can mediate the emergence and progression of human diseases. It has been shown that miRNAs can repress translation of mutual target genes in a concerted way. Thereby, a fine-tuned and adaptive target gene regulation can be achieved.

However, until now it has been unclear (i) which mechanisms underlie a collective target regulation and (ii) which miRNAs may even cooperate. After a comparative analysis of methods in computational miRNA biology this thesis describes two workflows that were designed to answer these two questions. In particular, the first workflow investigates mechanisms of collective target repression by miRNAs, while the second workflow is used to identify and analyse targets of synergistic miRNA regulation. Both workflows integrate bioinformatics and systems biology approaches with the goal for a maximum level of confidence with *in silico* predictions. More specifically, methods for data integration, the prediction of molecular interactions, modelling molecular complex structures, network analysis, and kinetic modelling are used here for the analysis of collective target regulation by miRNAs and for the prediction of cooperating miRNA pairs and their mutual target genes.

Two case studies are presented to demonstrate the efficiency of both workflows. In the first case study, the complex regulatory network of a miRNA target hub gene is analysed and predictive simulations are performed. These reveal a distinctive and fine-tuned regulation of the target hub gene for different cellular conditions. In the second case study, the human genome is analysed to predict targets of synergistic miRNA-mediated repression. The results suggest that the phenomenon of cooperative target regulation by miRNA pairs is a common cellular mechanism in humans which may be important in the context of cancer pathways.

The proposed workflows provide comprehensive tools for investigating mechanisms of post-transcriptional gene regulation and for the prediction of regulatory RNA interactions. These workflows can also be applied in the investigation of other gene regulatory networks and for predicting targets of cooperative miRNA regulation in other animal species.