How microRNA and transcription factor co-regulatory networks affect osteosarcoma cell proliferation.

Abstract:
Osteosarcomas (OS) are complex bone tumors with various genomic alterations. These alterations affect the expression and function of several genes due to drastic changes in the underlying gene regulatory network. However, we know little about critical gene regulators and their functional consequences on the pathogenesis of OS. Therefore, we aimed to determine microRNA and transcription factor (TF) co-regulatory networks in OS cell proliferation. Cell proliferation is an essential part in the pathogenesis of OS and deeper understanding of its regulation might help to identify potential therapeutic targets. Based on expression data of OS cell lines divided according to their proliferative activity, we obtained 12 proliferation-related microRNAs and corresponding target genes. Therewith, microRNA and TF co-regulatory networks were generated and analyzed regarding their structure and functional influence. We identified key co-regulators comprising the microRNAs miR-9-5p, miR-138, and miR-214 and the TFs SP1 and MYC in the derived networks. These regulators are implicated in NFKB- and RB1-signaling and focal adhesion processes based on their common or interacting target genes (e.g., CDK6, CTNNB1, E2F4, HES1, ITGA6, NFKB1, NOTCH1, and SIN3A). Thus, we proposed a model of OS cell proliferation which is primarily co-regulated through the interactions
of the mentioned microRNA and TF combinations. This study illustrates the benefit of systems biological approaches in the analysis of complex diseases. We integrated experimental data with publicly available information to unravel the coordinated (post)-transcriptional control of microRNAs and TFs to identify potential therapeutic targets in OS. The resulting microRNA and TF co-regulatory networks are publicly available for further exploration to generate or evaluate own hypotheses of the pathogenesis of OS (http://www.complex-systems.uni-muenster.de/co_networks.html).