Abstract

Background:
mi(cro)RNAs are a novel class of tiny regulators and play an important regulatory role by transcriptional degradation or translational repression of target mRNAs. So far, miR-143 is the only miRNA identified to have a regulatory role in human adipogenesis, with ERK5 as its only validated direct target. In addition, miRNAs directly targeting key regulators in other differentiation lineages were identified, such as miR-26a-Smad1 in osteogenesis and miR-124a-CEBP/a in hematopoiesis. This reflects the potential to discover also miRNA-regulated key players in the adipogenic lineage.

Objective:
The aim of this study is the identification of miRNA-mRNA networks targeting adipogenesis and obesity. For that, subcutaneous and visceral fat tissue probes of subjects with BMIs ranging from lean to severely obese state were available. The specific aims are: 1) profiling of miRNA and mRNA abundance; 2) identification of differentially expressed miRNAs and mRNAs; 3) identification of polycistronic miRNAs; 4) identification of miRNA-target mRNAs based on miRNA motifs in the 3`-UTR; 5) correlation analysis of paired miRNA-mRNA profiles; 6) combination of in vivo data with in vitro data; 7) enrichment analysis of miRNA-mRNA pairs for Gene Ontology terms and pathways; 8) generation of miRNA-mRNA networks; 9) identification of miRNAs potentially governing adipogenic key regulators.

Results:
The study identified differentially expressed mRNAs and miRNAs. Some co-expressed miRNAs were found to cluster within the genome and derive from a common primary, polycistronic transcript. The correlation analysis revealed both an anti-correlated and positively correlated miRNA-target mRNA network of comparable dimensions. By enrichment analysis generated miRNA-GO and miRNA-pathway networks indicate a miRNA-mediated regulation in many biological processes. An in-depth analysis of the anti-correlated interaction network elucidated a putative miRNA-mediated regulation of key players in adipogenesis and obesity. Furthermore, these miRNA-target interactions also identified biomarkers, related to insulin sensitivity. In conclusion, the identification of complex networks addressing the adipogenic program and insulin signaling in vitro and in vivo is the first step for the identification of novel, RNA-based drug targets for the treatment of obesity and related co-morbidities in the future.