Abstract

Brown adipose tissue (BAT) can combust energy to generate heat in the process on non-shivering thermogenesis, and may thereby serve as a future target for treatment of obesity. In addition, brite adipocytes can be induced in white adipocyte tissue (WAT) upon thermogenic stimulation. Despite an increase in research on thermogenic adipocytes, further investigations are required to characterize the transcriptional events underlying lineage-selective differentiation and functions of human adipocytes.

For the work presented in this thesis, we employed genome-wide sequencing to investigate transcriptional networks regulating lineage-selective differences between primary adipocyte progenitor cells from human WAT and BAT. By global analysis of the transcriptome and genomic regulatory regions, we compared lineage-selective differences between white and brown *in vitro* differentiated adipocytes and their progenitor cells. We found adipocyte progenitor cells to be highly preprogrammed for lineage-selective differentiation with substantial differences in gene expression and putative active enhancers at the progenitor stage. Adipocyte differentiation induced a common gene program related to general adipocyte functions in addition to lineage-selective gene expression. The lineage-selective gene programs in mature adipocytes overlapped with those of biopsies from human WAT and BAT, supporting biologically relevant preprogramming of progenitor cells. We used a novel bioinformatic tool to integrate transcriptomic data with data of putative enhancers and predicted candidate transcription factors which might regulate lineage-selective preprogramming and differentiation of adipocyte progenitor cells. Future studies are required to investigate the role of these transcription factors in lineage-selective gene expression.

In another project, we investigated the reprogramming in DNA binding of the transcription factor peroxisome proliferator-activated receptor γ (PPARγ) during browning of human white adipocytes by the PPARγ agonist rosiglitazone. We found that rosiglitazone induced the establishment of brite-selective PPARγ superenhancers, and we used these to predict novel transcriptional regulators of browning. We identified Kruppel-like factor 11 as an important regulator of rosiglitazone-induced browning and a possible interaction partner of PPARγ.

In summary, we provide novel genome-wide information on lineage-selective gene programs in human white, brite, and brown adipocytes.