SUMMARY

Transcriptional regulation forms the basis of cell type specificity and involves a complex network of combinatorial interactions between transcription factors, co-regulators, RNA polymerases and a large amount of proteins which regulate the chromatin structure at regulatory genomic elements throughout the genome. The complex interplay of this multitude of effectors allows spatial and temporal differences in gene expression, and thus each spezialized cell of an organism is characterized by its particular pattern of regulated gene expression. In the past two decades it has become increasingly recognized that the three dimensional organization of the chromatin in the nucleus greatly affects gene regulation and cell fate decisions and dissection of how three dimensional interactions between regulatory regions are established and regulated during lineage specification and differentiation will provide novel, important insights into the field of transcriptional regulation.

The work presented in this thesis is divided into two separate parts, which is presented in chapter two and three, respectively. In the first project we used a combination of functional studies and genome-wide sequencing technologies to describe the molecular mechanisms by which the novel anti-adipogenic regulator PBX1 inhibits adipocyte differentiation and describe the relationship between PBX1 and the key adipogenic transcription factor C/EBPβ. In this study we show that PBX1 differentially regulates gene programs related to adipocyte proliferation and differentiation from two highly distinct types of enhancers. Furthermore, we show that PBX1 primes poised adipogenic enhancers overlapping with C/EBPβ and functions at these enhancers to keep the chromatin inaccessible to adipogenic transcription factors in an antagonizing manner to C/EBPβ, thereby potently inhibiting adipocyte specific gene expression and differentiation.

In the other project, with the long term aim of describing the function and dynamics of the enhancer interactome during lineage specification and differentiation of mesenchymal stem cells, we established the novel technology high-throughput chromosome conformation capture (Hi-C) in combination with secuence capture of putative enhancer-anchored interactions. Although this project is ongoing, we have generated very high quality Hi-C libraries in un-stimulated MSCs and MSCs induced to differentiate into adipocytes. Although the enhancer capture process requires some adjustments to increase efficiency, initial analyses of captured enhancer-enhancer interactions suggest that the enhancer interactome is dynamicly rewired during adipocyte differentiation.