Epigenetic regulation of the epithelial to mesenchymal transition (EMT)

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer. Because of its resistance to chemotherapy and high capability to metastasize NSCLC is among the carcinomas with the lowest survival rate. EMT has been previously implicated as a cellular and mechanistic process that enables cancer cells to enter the bloodstream and metastasize.

The goal of this study is to identify the key genes and pathways that drive or enable the mesenchymal phenotype. Our approach was to localize and quantify differences in multiple histone modifications in a controlled experiment, since changes at the chromatin level have been shown critically important to cell differentiation, organism development, and other cancers.

Our model-system is a TNF-alpha and TGF-beta induced mesenchymal transition in the A549 NSCLC cell line. The A549 cells are grown in 3D cultures (SOMB) before the application of the two cytokines, which are thought to efficiently initiate and promote the complete reprogramming.

Our data-sets comprise paired epithelial (E) and mesenchymal (M) genome-wide maps of 18 histone modifications and whole genome expression microarrays. We have developed a methodology to compare multivariate epigenomic data sets between samples and derived differential epigenetic features (DEF) for known genes and putative distal regulatory loci.

We show that functionally related genes have similar DEFs and that the patterns correlate with changes in gene expression. Three signatures enrich for genes related to EMT and malignant phenotypes in general. Multiple genes within the EMT clusters are known markers of the transition, which implies that epigenetic reprogramming coincides epithelial phenotype switching.

Enhancers can be broadly divided into activated and repressed states, each associated with a specific set of transcription factors. Further we show that EMT-related genes form a tight protein-interactions network with centers at critical overexpressed transcription factors, and modules related to the activated signalling pathways, which suggests a positive feedback loop during the phenotype switch.