Transcription factor and gene regulation

The regulation of gene expression is fundamental to many important biological processes such as cell growth, proliferation, differentiation, and response to the extracellular environment. The regulation of transcription is the most important step in control of gene expression. This involves binding of transcription factors (TFs) to their cognate DNA regulatory elements and activating or repressing transcription. The transcriptional program of a cell is highly dynamic and responsive to intracellular as well as environmental signals. Therefore, identification, characterization and validation of these DNA regulatory elements is among the most important and challenging tasks for biologists in the post-genome era.

A case for developing novel approach to build transcriptional regulatory network

Current approaches for predicting and building transcriptional regulatory networks are limited in their applicability. Most of these works have exploited the co-occurrence of promoter motifs to predict interacting transcription factors to model expression regulation and to detect regulatory modules and some of these works impose specific distance constraints between co-occurring motifs. However, very few existing methods are designed to be applied on a genome-wide scale without prior knowledge about sets of interacting TFs or sets of co-regulated genes.

A case for studying transcriptional regulatory network in lung and breast cancer

Alteration of gene regulation is a characteristic feature of disease conditions such as cancer. Genetic anomalies within cancer cells co-operate with extra tumoral micro-
environment to generate a transcriptional program unique to a tumor type. Predictably, this must involve differential expression and binding of a select group of transcription factors within each tumor type, therefore giving identity to cancer transcriptome. Metastases or the dissemination and growth of primary tumor to distant sites in body are the most lethal aspect of cancer and accounts for approximately 90% deaths due to cancer. Among all known cancers, lung cancer is a leading cause of death in men and women worldwide and accounts for one fourth of cancer deaths. Among women, breast cancer is one of the leading killers. Primary tumors in lung frequently metastasize to brain, bone, adrenal gland and liver. Primary breast tumors metastasize to lung, brain and bone among other organs. However, the regulators of metastatic dissemination are largely unknown.

A case to test interplay between nucleosome and transcription factor binding sites in progression of cancer

It is widely believed that modifications in chromatin leading to exposure of target sites precede and thereby control DNA binding of transcription factors. This posits spatio-temporal chromatin-guided recruitment of regulatory factor(s), which when coordinated in a genome scale translates to combinatorial regulatory signals. Ultimately that produces complex functional changes like progression of cancer.

Aims and objectives of the study

The study aimed to identify transcription factor pair and there coordination in regulation of genes that change during cancer progression in lung and breast cancer. Next, the inter-play of transcription factor binding site and nucleosome positions that may be important in metastasis was also studied.
The specific objectives of the study were as follows:

1. Building positional network of transcription factors binding sites from predicted as well as available experimental information about target sites.
2. Test the functionality of in silico positional network in metastasis of breast and lungs
3. Building and analyzing transcriptional regulatory network centered on the metastases suppressor NME2 in breast and lung cancers.

A combination of gene expression, chromatin immunoprecipitation followed by de-novo sequencing (ChIP-seq), and protein-protein interactions datasets were used to achieve first objectives. To identify regulatory network centered to NME2, ChIP-seq and transcriptome profiling was performed. To test interplay between NME2 binding site and nucleosome position, mapping of nucleosome positions to putative promoter regions was performed using tiled promoter microarrays.