ABSTRACT

Computational methods for modeling and identification of cis-regulatory elements have been developed over the past two and a half decades. However, current approaches for predicting and building transcriptional regulatory networks are limited in their applicability. This work focused on a novel combinatorial approach to identify regulatory network by analyzing transcription factor binding site position, evolutionary conservation and expression data for transcription factors. Next, this approach was applied in studying the transcriptional regulators of cancer metastasis which is the main cause of mortality in cancer patients. In particular, the transcriptional regulators of lung and breast cancer metastasis were studied in more detail as these cause highest number of cancer related deaths among men and women worldwide respectively. Further, the transcriptional regulators affecting drug resistance in cancer was also explored. Based on the analysis of NCI-60 cell lines for drug resistance, the computational approach presented here identified many novel combinations of transcription factor (TF) pairs which control the effects of chemotherapeutic drugs on cancer cells. Experimental analysis of cell viability in breast cancer cell lines with targeted silencing of identified TF pair was consistent with prediction. Next, large scale analysis of candidate regulators of metastasis identified Non-metastatic 2 (NME2)/ NM23 H2 as a key factor for cancer metastasis. Using genomic approaches such as chromatin immunoprecipitation followed by de-novo DNA sequencing (ChIP-seq) and gene expression microarrays in metastatic and non-metastatic cells, this study characterized the genomic regions bound, the consensus motif, and the target genes of NME2. Nucleosome mapping analysis across human gene promoters further yielded insights into binding of NME2 to target sites. In summary, this study used a combination of computational and genomic approaches for identification and characterization of transcriptional regulators of cancer metastasis.