

**Signed weighted gene co-expression network analysis of transcriptional regulation in murine embryonic stem cells.**

<b>Journal:</b>	BMC Genomics
<b>Publication Year:</b>	2009
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<b>PubMed link:</b>	19619308
<b>Funding Grants:</b>	Generation of clinical grade human iPS cells , In vitro reprogramming of mouse and human somatic cells to an embryonic state

**Public Summary:**

Recent work has revealed that a core group of transcription factors (TFs) regulates the key characteristics of embryonic stem (ES) cells: pluripotency and self-renewal. Current efforts focus on identifying genes that play important roles in maintaining pluripotency and self-renewal in ES cells and aim to understand the interactions among these genes. To that end, we used a novel bioinformatics analysis tool to identify pluripotency and differentiation related genes. We found a pluripotency module and a differentiation module and confirmed the importance of these modules by incorporating genome-wide TF binding data for key ES cell regulators. Interestingly, we find that the pluripotency module is enriched with genes related to DNA damage repair and mitochondrial function in addition to transcriptional regulation. Our systems biologic re-analysis of gene expression, transcription factor binding, epigenetic and gene ontology data provides a novel integrative view of ES cell biology.

**Scientific Abstract:**

**BACKGROUND:** Recent work has revealed that a core group of transcription factors (TFs) regulates the key characteristics of embryonic stem (ES) cells: pluripotency and self-renewal. Current efforts focus on identifying genes that play important roles in maintaining pluripotency and self-renewal in ES cells and aim to understand the interactions among these genes. To that end, we investigated the use of unsigned and signed network analysis to identify pluripotency and differentiation related genes. **RESULTS:** We show that signed networks provide a better systems level understanding of the regulatory mechanisms of ES cells than unsigned networks, using two independent murine ES cell expression data sets. Specifically, using signed weighted gene co-expression network analysis (WGCNA), we found a pluripotency module and a differentiation module, which are not identified in unsigned networks. We confirmed the importance of these modules by incorporating genome-wide TF binding data for key ES cell regulators. Interestingly, we find that the pluripotency module is enriched with genes related to DNA damage repair and mitochondrial function in addition to transcriptional regulation. Using a connectivity measure of module membership, we not only identify known regulators of ES cells but also show that Mrpl15, Msh6, Nrf1, Nup133, Ppif, Rbpj, Sh3gl2, and Zfp39, among other genes, have important roles in maintaining ES cell pluripotency and self-renewal. We also report highly significant relationships between module membership and epigenetic modifications (histone modifications and promoter CpG methylation status), which are known to play a role in controlling gene expression during ES cell self-renewal and differentiation. **CONCLUSION:** Our systems biologic re-analysis of gene expression, transcription factor binding, epigenetic and gene ontology data provides a novel integrative view of ES cell biology.

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