

Mapping Interactions at Genome Scale for a Specific Biological Context: A Case Study in Epithelial-Mesenchymal Transition

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Epithelial to Mesenchymal Transition (EMT) is important in embryonic development, cancer progression and fibrosis. Complex molecular networks control EMT and the reverse process (MET), including interactions between canonical signaling pathways. Indeed, many genes have poorly characterised function and systematic phenotyping indicates that pleiotropy is typical rather than exceptional. Therefore, a data-driven network biology approach is useful for understanding context-specific control of EMT/MET and overlapping processes.

Harnessing multiple orthogonal functional genomics datasets using a novel machine learning approach we predicted a systems-wide map of gene function in EMT/MET containing 10,592 genes and 1,968,058 context-specific biochemical relationships (EMT_MAP). We discovered novel genes and modules in embryonic EMT/MET as well as in renal cancer metastasis, by using the EMT_MAP framework for graph-theoretic analyses incorporating Snail induction time course data in embryonic stem cells (ESCs) and The Cancer Genome Atlas. Network analysis also identified genes not previously associated with renal cancer that risk stratified patients by overall survival.

In order to generate EMT_MAP we developed CoSNI (Context-Specific Network Inference) a novel machine learning approach, integrating transcriptomic, quantitative proteomic and chromatin datasets in order to obtain a context-specific signalling network. CoSNI performs filtering to derive a context-specific gold standard, followed by classification. CoSNI performed well on blind test data (ROC AUC 0.86).

Analysis with EMT_MAP identified novel subnetworks that control EMT/MET as well as cancer progression. We predicted a novel druggable target in epithelial and mesenchymal phenotype switching, which was validated in an organotypic invasion assay.