A Multiomic Approach to Mathematical Modeling of Gene Regulatory Networks in Multiple Myeloma

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Input

16,738 Genes

RNA-Seq

Differentially Expressed Gene (DEG) Cluster

Ex Vivo Drug Sensitivity

Transcriptomic Map for MM

GRN

Output

Biomarkers

Personalized Therapy

Model

Accuracy

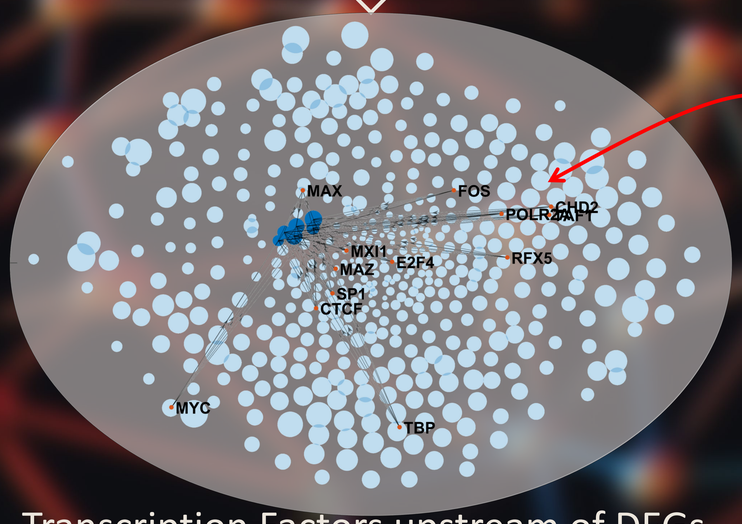
Chromatin

Variability

Mechanism of Resistance

Novel Combinations

DEG



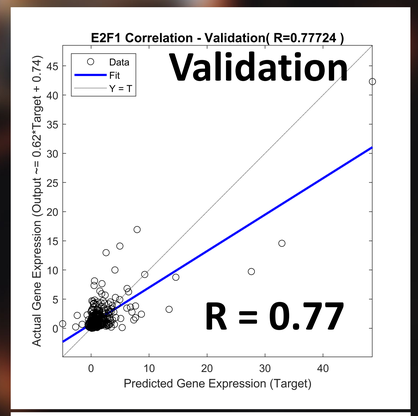
Transcription Factors upstream of DEGs

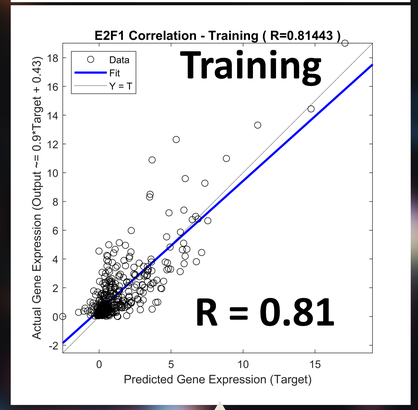
Publicly Available Databases

ENCODE/ChEA ChIP-Seq

PhosphoSitePlus Proteomics

SelleckChem Kinase Inhibitors





Parameter Estimation

Transcription

$$\frac{dG_i^j}{dt} = -K_{rd}^j G_i^j + K_{RNA}^j Chr_i^j \left(\sum_{T=1}^{n_T} \Pi_T^j \alpha_{Ti} P_T^j \right)$$

Translation

$$\frac{dP_T^j}{dt} = K_{rb}^j G_T^j - K_p^j P_T^j$$

PTM

$$\frac{d\Pi_T^j}{dt} = -\gamma_T \Pi_T^j + \sum_{l=1}^{n_K} \beta_{KT} P_K^j (1 - \delta_{KI})$$

BACKGROUND: Multiple myeloma (MM) is a treatable yet incurable bone marrow–resident plasma cell malignancy. The study of mechanisms of therapy resistance in MM are poorly understood due to inter-patient tumor heterogeneity and wide-spread use of drug combinations. We describe a multiomic computational approach to create patient-specific gene regulatory networks from matching RNA-seq and *ex vivo* drug sensitivity data from primary MM samples to a panel of 100+ standard of care and experimental MM drugs, in addition to publicly available ChIP-seq and proteomic databases (ENCODE/ChEA/PhosphoSitePlus-PSP).

METHODS: A topological map of MM transcriptome was generated using t-SNE and fuzzy c-means clustering on z-normalized expression of 16,738 genes for 844 MM patient tumors. Gene Set Enrichment Analysis (GSEA) of *ex vivo* drug response, and matched gene expression of MM patients, identified differentially expressed gene (DEG) clusters.
As a proof-of-principle, we have investigated DEG clusters identified by GSEA to correlate with *ex vivo* resistance to proteasome inhibitors (PIs). Using publicly available ChIP-seq databases, we identified regulatory proteins (RPs) upstream of DEG clusters. Kinases phosphorylating these RPs were identified from PSP database, generating a cascading network of DEGs, RPs, and kinases described by a model of ordinary differential equations representing transcription, translation, and post-translational effects.

RESULTS: We identified 197 DEGs associated with PI-resistance in MM, 13 upstream RPs, and 45 kinases (17 druggable by kinase inhibitors). The proposed model was trained with expression data of upstream RPs and kinases from 430 randomly selected patients and validated in a 414-patient cohort. 177/197 DEGs showed a strong linear (Pearson's) correlation ($R \geq 0.5$) in the validation cohort. CDK inhibitors Seliciclib and Dinaciclib were predicted to effect DEGs with statistical significance (0.05) in 87.5% and 84.9% patients using a paired t-test. Dinaciclib's role in 16 PI-resistant patients was functionally validated *ex vivo*, where 10 patients show synergy with PIs.

CONCLUSION: This model is a tool to infer mechanisms driving therapy resistance in MM and is a proof-of-principle of a clinical decision support tool to inform patient-specific targeted therapies in MM.