Predicting kinase inhibitor induced cardiotoxicity using transcriptomics and clinical risk scores

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Objectives: A major side effect of several kinase inhibitors (KIs) is cardiotoxicity (CT), manifesting as loss of contractile function and heart failure [1]. There is an urgent need to minimize KI-associated CT risk in individual patients, and for newly developed KIs. However, the underlying mechanisms KI-associated CT are still poorly understood [1]. We aimed to derive predictive signatures for CT risk, based on regression analyses of transcriptomic and clinical CT risk data.

Methods: Human primary cardiomyocyte cell lines (n=4) were treated with 24 KIs, followed by mRNAseq profiling. Z-scores for the relative risk of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), ventricular dysfunction (VD) and undefined cardiotoxicity (CTU) were derived through mining of the FDA Adverse Event Reporting System database. Individual gene expression based metrics (IGEMs) and weighted correlation network derived signatures (WCNMs) were computed for each drug. These metrics were then associated with CT clinical risk scores using elastic net regression and leave-one-out (LOO) cross-validation.

Results: IGEM based metrics best predicted HCM with a LOO $R^2$ of 0.78, and WCNM-based metrics best predicted DCM with a LOO $R^2$ of 0.92. Predictive WCNR clusters ranged from 12 to 61 genes and distinctly enriched for various cytoskeletal processes, cell shape regulation, insulin-like growth factor receptor signaling, oxidative phosphorylation, and different metabolic processes.

Conclusion: We have generated quantitative expression based signatures associated with clinical risk for cardiotoxicity. The biological mechanisms associated with the individual predictors may provide global insights in mechanisms underlying KI-associated CT, and its mitigation.

References:
