Combined kinome and transcriptome profiling reveals broad and distinct activities of cardiosafe (erlotinib) and cardiotoxic (sunitinib, sorafenib) kinase inhibitors

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Introduction: Despite putative selectivity for their respective molecular targets, numerous kinase inhibitors (KIs) have unanticipated cardiotoxicity. Mechanisms underlying KI cardiotoxicity remain unclear, largely because the molecular consequences of cardiac KI exposure are unknown. We developed a platform to analyze kinase activity using Multiplexed Inhibitor Beads (MIBs) with mass spectrometry (MIB-MS), allowing simultaneous determination of the activity of over 80% of the expressed kinome. Combining MIB-MS with RNAseq transcriptome profiling may offer a novel approach to understanding the mechanisms underlying the known cardiotoxicity of extant KIs and predicting cardiotoxicity of KIs in the pre-clinical stages of drug development.

Methods: We treated female FVB mice (n=5 per group) with saline or erlotinib (50 mg/kg/d), sunitinib (40 mg/kg/d), or sorafenib (30 mg/kg/d) by gavage daily for 2 weeks. Echocardiograms were done at Days 0, 7, and 14. Heart tissue was processed for MIB-MS and RNAseq.

Results: Fractional shortening on Day 14 echocardiogram was unchanged in erlotinib-treated mice, and variably but significantly decreased after sunitinib and sorafenib. MIB-MS revealed broad reproducible kinome changes: erlotinib (70 kinases upregulated, 18 downregulated); sunitinib (54 up, 30 down); sorafenib (62 up, 18 down). Metabolic kinases were affected disproportionately. RNAseq revealed significant changes in over 2500 genes in each group. Cardiotoxic KIs shared upregulation of 5% of transcripts, with a pronounced upregulation of genes involved in transcriptional regulation (Gene Ontology: 23% of affected genes, $p = 10^{-18}$) and chromatin remodeling (5%, $p = 10^{-10}$).

Conclusions: The highly selective and cardiosafe KI, erlotinib, induced as many changes in the cardiac kinome and transcriptome as the multi-targeted cardiotoxic KIs, sunitinib and sorafenib. These findings underscore the broad molecular consequences of therapeutic kinase inhibition and indicate that cardiotoxicity does not result solely from the breadth of KI targeting. Adverse metabolic and transcriptional effects may predict cardiotoxicity.